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In

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For the examinations to be conducted in

August 2014

Department of Clinical Haematology

Christian Medical College, Vellore.

Tamil Nadu, India.

A prospective study of the demographic profile and clinical outcomes of newly diagnosed patients with acute myeloid leukemia at our centre .

CERTIFICATE

This is to certify that the dissertation entitled "**A prospective study of the demographic profile and clinical outcomes of newly diagnosed patients with acute myeloid leukemia at our centre**" is a bonafide work of the candidate, Chepsy C Philip, of Christian Medical College in partial fulfillment of the University rules and regulations for award of Doctorate of Medicine (higher specialty) in Clinical Haematology under my guidance and supervision during the academic year 2011-2014.

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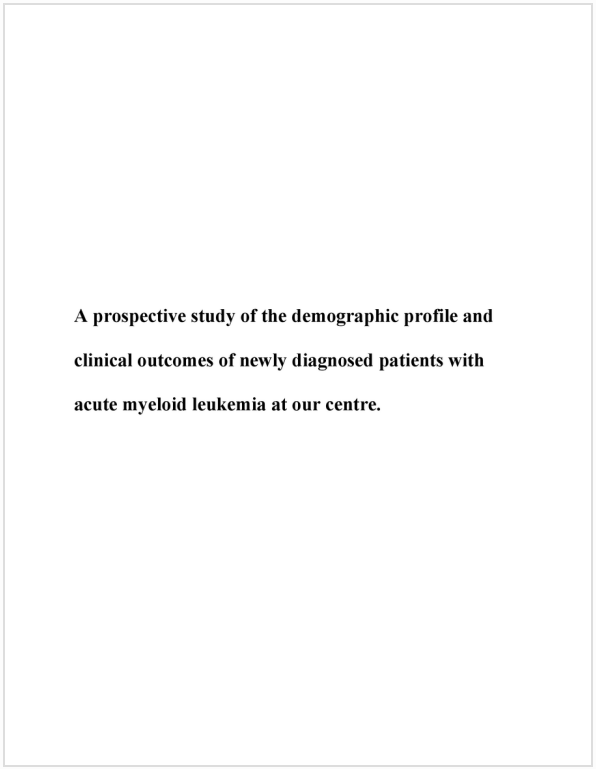
A prospective study of the demographic profile and clinical outcomes of newly diagnosed patients with acute myeloid leukemia at our centre.

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Sub: **Fluid Research grant project NEW PROPOSAL:**
A prospective study of the incidence and clinical outcomes of newly diagnosed patients with acute myeloid leukemia at our centre and evaluation of WTI expression as a prognostic marker.
Dr. Chepsy C Philip, PG Registrar, Haematology, Dr. Vikram Mathews, Dr. Poonkuzhali Balasubramanian, Dr. Biju George, Dr. Auro Viswabandya, Dr. Aby Abraham, Dr. Rayaz Ahmed, Dr. Alok Srivastava, Haematology.

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Dear Dr. Chepsy C Philip,

I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

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Secretary (Ethics Committee)
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CC: Dr. Vikram Mathews, Department of Haematology

ACKNOWLEDGEMENT

(My Work Is For A King)

Foremost my gratitude to the Almighty; only with whose mercy, this work has been possible.

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Last but not least, my gratitude to the patients and families whose data has been analyzed in this study.

CONTENTS

TITLE OF THE ABSTRACT : A prospective study of the demographic profile and clinical outcomes of newly diagnosed patients with acute myeloid leukemia at our centre.

DEPARTMENT : Clinical Haematology

NAME OF THE CANDIDATE : Chepsy C Philip

DEGREE AND SUBJECT : DM (Clinical Haematology)

NAME OF THE GUIDE : Vikram Mathews

AIM / OBJECTIVES:

1. Study the incidence and demographic profile of newly diagnosed adult acute myeloid leukemia at our centre

2. Evaluate treatment and clinical outcome of the patients treated at our center.

MATERIAL AND METHODS:
Newly diagnosed patients at the department of clinical haematology were administered a questionnaire at presentation. Patients proceeding with therapy were prospectively followed up and outcomes noted. Patients who did not proceed with treatment were re-interviewed subsequently to confirm status and treatment. Descriptive statistics were calculated for all variables. Differences in proportions were assessed using the $\chi 2$ or Fisher exact statistic. Differences in means were tested using a Mann-Whitney-U test or t-test as appropriate. The probability of survival was estimated with product-limit method of Kaplan and Meier for overall survival and event-free survival and compared by the log-rank test.

RESULTS:
There were 318 newly diagnosed patients were evaluable for the study. The median age at presentation was 40(1-79) years. 95 (29.9%) patients proceed to treatment.148 (69.2%) patients had AML with intermediate cytogenetic risk. 174(81%) patients did not proceed with treatment due to inability to finance the costs of therapy. CR/CRi was achieved in 13(59.1%), 37(58.7%) and 1(10.0%) patient in the paediatric, adult and elderly group respectively; (P=0.005). The most common organism in the blood cultures with isolates were [GNB] gram negative bacilli [37(39%)]. The one year overall survival in those treated, was 58.7% ± 6.0% at a median follow up of 3 months.

CONCLUSIONS:
The median age of patients with AML noted in our study is three decades earlier than that reported in the literature. The inability to finance treatment costs and inability to accompany the patient for the duration of therapy are the main reasons in declining therapy identified in our study. Another major concern is the incidence of infections both bacterial and fungal, higher than reported in literature with invasive fungal disease is present in greater than 50% of individuals who die during induction.

Key Words: Demographics, AML, Treatment.

INTRODUCTION:

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of haematopoietic progenitor cells unable to differentiate and respond to normal regulators of proliferation. The standard of care in treatment has remained induction chemotherapy with anthracycline and cytosine followed by consolidation. In adults with acute myeloid leukemia (AML), intensive chemotherapy achieves complete remission (CR) rates ranging from 50% to 80%. Despite these encouraging results, the majority of patients with the diagnoses who present at our centre do not receive conventional therapy. Recent progress into the biology of the disease has involved dose modifications within the current standards of care .These improvements though significant might not contribute into improving treatment outcomes in a resource restricted economy like ours where costs of therapy are unaffordable to the majority. In an earlier study from our centre it was recognized that only 20 % of patients with AML proceed to receive conventional therapy. We need to identify factors which influence treatment decisions and outcomes in addition to dose modifications to be socially relevant.

One of the clinical challenges lies in accurately predicting and prognosticating those who relapse and those who attain cure by better detection of Minimal Residual Disease (MRD).It is also recognized that treatment outcomes amongst similar patient groups differ. WT1 is a uniformly available disease marker that needs to be explored as a tool for MRD.

An analysis of the epidemiology, clinical features and outcome of the disease would enable an understanding of the disease in our population. Such an analysis would also enable caregivers and treatment providers to plan and allocate therapeutic strategies to optimize treatment in our patients with Acute Myeloid Leukemia.

REVIEW OF LITERATURE

Acute myeloid leukemia is a clonal hematopoietic disorder characterized by an impairment in self-renewal, differentiation and proliferation of the myeloid stem cell compartment due to acquired somatic mutations(1).It is more common with advancing age; and, as the population ages, more cases of AML are expected (2-4).

Currently AML is categorized based on the World Health Organization (WHO) classification into four major subgroups .The first group features recurrent genetic abnormalities of prognostic significance. The second group is characterized as AML with Myelodysplasia-related changes and the third group is classified as therapy-related myeloid neoplasms. The fourth is the group of AML not otherwise specified (NOS), the definition being based on morphological , cytochemical and immuno-phenotypic features, representing the earlier FAB classification(5).

It is recognised to evolve by a multistep mechanism involving the occurrence of two classes of mutations. One group (class I) comprises mutations that activate signal transduction pathways and thereby increase the proliferation or survival, or both, of hematopoietic progenitor cells. The other complementation group (class II) comprises mutations that affect transcription factors or components of the cell cycle machinery and cause impaired differentiation (6).Mutations in KIT, FLT3, and NRAS fall into the class I mutations. Class II Mutations are those involving mutations in the core binding factorβ, RUNX1,MLL, BAAL, Wilm's tumor gene (WT-1),

CCAAT/enhancer-binding protein α (CEBPα), and Nucleophosmin 1 (NPM1)(7, 8). A new class (class III) of mutations involving IDH1, AXL etc. affecting epigenetic regulation is also being increasingly recognized(9).

Acute Myeloid leukemia- Therapeutics

Despite the ability to achieve complete remission rates of 50-80% following induction; the current five-year survival rates of patients under age 60 who receive intensive chemo -therapy for AML range from 30% to over 40%(10-16).

With more information being available about the prognostic factors, molecular biology and molecular genetics of acute myeloid leukemia (AML) there has been an improved understanding leading to modifications in therapy.(17-20)However for the past 30 years, except for the increasing use of allogeneic bone marrow transplantation because of an ever-increasing unrelated donor pool and the use of reduced-intensity conditioning for older patients and those with co morbidities;treatment of AML has consisted of the combinations of anthracyclines with cytarabine (21, 22).

Therapy consists of two phases:

i. Induction- The goal is to achieve a complete remission (CR), defined as bone marrow with less than 5% blasts, an absolute neutrophil count (ANC) greater than 1000/mm^3, with a platelet count greater than 100 000/mm^3(16).

CR is the only response reported consistent with cure or at least an extension in survival(23).

For the past three decades induction has essentially consisted of a combination of anthracycline with cytarabine. Traditionally the anthracycline used has been daunorubicin. Comparisons amongst various anthracyclines and dose modifications have been tried(24).

Several studies have compared alternatives to daunorubicin without convincingly establishing benefit. However, there are questions regarding the dose equivalence of daunorubicin, mitoxantrone and idarubicin. Improvements may show itself not only by the proportion of patients entering complete remission, but also in reducing relapse. The addition of a third drug has been tested with no convincing benefit mixed results for etoposide, mitoxantrone or thioguanine. Their benefits may cost more procedural mortality with failure to deliver post induction therapy (25-27).

Dose escalation of daunorubicin has also been explored with a recent study claiming a potential new standard of care at a dose level of 90 mg/m^2(28).A criticism of this study has been the outcomes of the control were lower than expected. A comparison of an 80mg/m^2 daunorubicin with idarubicin showed no difference suggesting that the traditional dose of daunorubicin may be suboptimal but equivalent to idarubicin at 12 mg/m^2(29-31). Several attempts have been made to modify the dose and the duration of cytarabine but with no conclusive improvement in overall survival (OS). Cytarabine irrespective of daily dose of 200 mg/m^2 by continuous infusion , twice per day bolus, doubling to 400 mg/m^2, extending to 10 days or escalating to a $3g/m^2$, has not made a major impact(32).Treatment with fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin though shown to reduce the relapse rate without improving CR is at the cost of more myelosuppression and ability to deliver post induction treatment(31).

ii. Consolidation- The aim of the second phase of therapy is to prolong the complete remission.

Various options for consolidation include:

a) Intensive non-myeloablative consolidative chemotherapy

b) Autologous stem cell transplantation.

c) Allogeneic stem cell transplantation.

Intensive consolidation chemotherapy associated with the lowest treatment related mortality (TRM); has the highest risk of disease relapse in comparison to an allogeneic SCT, which in contrast is associated with the lowest risk of disease recurrence, but with the highest risk of TRM. (31)An autologous SCT has an intermediate risk of TRM and relapse risk in two the other two options (31, 33-35).

The option for the type consolidation therapy is strongly influenced by the cytogenetic risk group. The good, intermediate and adverse groups have a risk of 25%, 50%, and ≥ 70% of relapse and a corresponding 4-year probability of survival of ≥ 70%, 40% - 50%, and ≤ 20%(36). Parameters, such as age, response to induction chemotherapy, white blood cell count at diagnosis and type of consolidation therapy; alter these predicted outcomes (18-20).

In view of the TRM of 15% to 30%; an allogeneic SCT is not considered in the good-risk group, when repetitive cycles of high-dose non-myeloablative consolidation chemotherapy can achieve long-term DFS greater than 70% with a less than 5% TRM (11, 37).

In contrast the choice would be to proceed if possible with an allogeneic SCT in CR1 in the unfavorable-risk group, not because of the data supporting this, but rather due to the dismal outcome with either autologous SCT or following chemotherapy alone. The intermediate-risk group representing close to 40% to 50% of all patients with AML has less clearly defined options (11).

Prognostic factors-

The treatment outcomes are influenced by various prognostic factors (17-20). Age, cytogenetics, Performance scores, comorbidities and socioeconomic status considered prognostic factors (15, 18, 38-40)(Table A).

The Swedish Acute Leukaemia Registry , the largest national population based unselected series has shown that age has a strong prognostic impact , regardless of management(41).

Our current understanding of prognostic factors is summarised in Table A.

The most important implication of the prognostication is the decision to transplant patients in first complete remission(42).Allogeneic HSCT as a post remission strategy is associated with the lowest rates of relapse (43).This benefit is attributable to both the potent graft-versus-leukaemia (GVL) effect and the high-dose therapy of standard conditioning regimens(44-49).

Once a patient has been in remission for 3 years though, the likelihood of relapse declines sharply to $\leq 10\%$(50).

Table A- Prognostic factors in AML(51)

	Standard	Intermediate	Unfavourable	Uncertain
A. Patient related				
Age			>50 >65 >75	
Performance status			Poor	
Co morbidities			Multiple	
Socioeconomic status	White collar			
Race and gender			African American men	
B. Disease related				
WBC count			More than 20/ 30/ 50/ 100,000/μL	
Immunophenotype			CD7/ 11b/ 14/34, HLA-DR	
Cytogenetics (according the MRC)	t(15;17)(q22;q21), t(8;21)(q22;q22), t(16;16)(p13;q22)inv(16)(p13q22)/ Regardless of additional cytogenetics	Entities not classified as favourable or unfavourable	abn(3q) [excluding t(3;5)(q25;q34)], inv(3)(q21q26)/t(3;3)(q21;q26), add(5q)/del(5q), -5, t(9;22)(q34;q11), -17, and abn(17p), -7,add(7q)/del(7q), t(6;11)(q27;q23), t(10;11)(p11˜13;q23), other t(11q23) [excluding t(9;11)(p21˜22;q23) and t(11;19)(q23;p13)], Complex (≥4 unrelated abnormalities) Excluding cases with favourable karyotype	
Molecular diagnosis:				
CBF AML	-		t(8;21) + KIT mut	inv(16) + KIT mut
Normal karyotype	-		FLT3-ITD	-
-	NPM1 mut FLT3 wt	-	TET2	-
--	CEBPA dm FLT3 wt	-	DNMT3A	NRAS+KRAS
-			TP53 mut	WT1
-			MDR1 overexposed	MLL-PTD
Secondary AML (in addition to karyotype)		t-AML in int. cytogenetic group	t-AML in unfavourable group	t-AML in favourable group
C. Response related				
Day 14–16 marrow	<5% blasts		≥5% blasts	-
			In a cellular BM	-
PB blast clearance	Early	-		
MRD	Negative		Positive	-

WT1 (Wilm's tumour 1 gene)

Recurrence is common in the majority of the patients with AML without allogeneic transplantation. Leukemia stem cells display resistance to chemotherapy and it may be an important reason why it is difficult to eradicate AML cells in the majority of patients. In this context; the potential of minimal residual disease (MRD) as a tool to identify response to treatment would improve therapeutic strategies.Current methods to evaluate MRD involve the follow up of known molecular markers. Patients with persistent elevated levels in fusion transcripts at the end of therapy or associated with transcripts reappearance after molecular remission are prone to early relapse(52, 53). Alternative options are based on the detection of mutated genes, like FLT3-ITD and NPM1 or over expressed genes, like WT1 (54).

WT1 (Wilm's tumour) was identified originally for its involvement in the pathogenesis of Wilm's tumor and has been shown at high levels of expression in several hematopoietic tumours, including AML(55-61). Wilm's tumor gene WT1 encodes a transcription factor which plays an important role in cell growth and differentiation(62, 63).However, the clinical utility of WT1 monitoring has been controversial, partly reflecting differences in assay performance to date(64-69).It is reported that monitoring by real-time quantitative polymerase chain reactions (RQ-PCR) to detect leukaemia-specific targets (i.e., fusion gene transcripts such as PML-RARA or mutations such as that in NPM1) would identify those patients at the highest risk of relapse ; thereby providing an opportunity for early treatment intervention (54, 70).There is interest in the potential for WT1 assessment to provide a target for sequential MRD monitoring, particularly as a tool directed at need for treatment modification, as it is uniformly expressed irrespective of cytogenetic and molecular classification.

Determining the kinetics of WT1 transcript reduction following induction chemotherapy however provides a key prognostic factor, distinguishing patients at differing risk of relapse, within cytogenetically defined risk groups.

The European Leukemia study noted that WT1 transcript reduction post induction might predict the relapse risk. The levels of WT1 were assessed after chemotherapy-induced morphologic CR, in peripheral blood (PB), and BM in patients with AML. In the multivariate analysis it was noted that a ≥ 2-log MRD reduction in WT1 expression was associated with a significantly lower cumulative incidence of relapse (P = .004). However only in 13% and46% of BM and PB samples, respectively, were the levels of WT1 sufficiently over expressed, in comparison to normal samples, allowing for a prognostic stratification. Also, as WT1 is expressed in some stages of haematopoietic development, but not others, the expression in leukaemia could possibly enable to identify the cell of origin of the malignancy(71, 72).

Though concerns about the confounding role of the physiologic background of WT1in normal PB and BM remain to be addressed, it can be exploited as a potential marker to establish the presence, persistence, or reappearance of leukemia (65) .

INDIAN SCENARIO

The epidemiology of AML in India is yet to be comprehensively studied; where the results of progress made into the biology of the disease as well as in its treatment might not make an impact on the majority of the patients. The limited data available on the AML profile in India are from single centre experiences(73, 74).

With a population of 1200 million the actual cancer burden in our country might account to large number of patient cases even though accurate statistics are unavailable. The pattern of leukemia's observed in India as reported in literature is different from what is reported from the rest of the world (75-78).The age standardized incidence rates are lower and they occur at an earlier age (79).Chronic leukemias are reported as more prevalent amongst adults in India (79, 80). Among the individual leukemias chronic myeloid leukemia is the most prevalent(76). In the first report on the incidence of cancers in 20 population based registries, a male predominance amongst leukemias and a higher prevalence in the urban settings is noted(57).

Despite the advances and progress in our understanding; we fail to provide adequate primary health care to the majority of our patients(81).

In a report on health care in India it was recognised that few patients have access to specialized treatment(82). A skewed cultural understanding of ill health and well-being, extent of socio-economic disparities, reach of health services, quality and costs of care and lack of social support could amplify the inadequacy in specialised treatment (83-86) .

There exists a paradox in the Indian health scenario. India has access to highly skilled technical communities that can translate ambitious projects into practical reality , however health is rarely a decisive political issue and as a nation our performance is dismal with regards to health parameters(87, 88). A few things need to be understood about the Indian public health system(89).

1 There is yet to be developed comprehensive universal health coverage as practiced in the west(86, 90).
2 In our country despite a multitude of public policies only 1.2 % of the GDP is

India's public spending on health(91).

3 Health schemes implemented by the government fail to reach the under privileged(92, 93).

4 Only 243 million of India's 1.2 billion citizens are covered under Government health insurance schemes and only 10% of our population Indians have some form of health insurance with about 40% of Indians having to borrow money or sell assets to meet their health care expenses(94-96).

5 An estimated 55% of the population in India is poor by the multidimensional poverty index(87).

6 Only 7% children in India receive the minimum acceptable diet set by the WHO(44).

7 Out of pocket expenditure still remains close to 80 % of all spending(8, 97).

8 India is ranked a low 136 in terms of the human development index (HDI) which assesses long term progress in health and social well-being(98).

9 The annual per capita net national income in real terms is estimated at Rs.39, 168/-(99).

It is very imperative to understand this so that appropriate treatment strategies could be planned in the context of our health system.

There have however been no large scale descriptive studies tackling the pattern and patient behavior in patients with acute myeloid leukemia which needs to be characterized to improve treatment strategies.

With costs of primary induction estimated to be around ₹ 4 to 6,00,000/-; it is easy to understand that most patients in our country will not afford treatment; and a provision of an efficient, affordable and equitable treatment policy for our population will involve much more than the quoting and reporting the treatment progress quoted from western literature.

Identifying pretreatment factors in acute myeloid leukemia is also equally important in improving our treatment outcomes. As previously noted in a study from our centre treatment outcomes in those who proceed with treatment are similar to those reported in literature. Therefore there is a strong need to characterize the disease process and identify factors which may provide prognostic information which influence responsiveness to chemotherapy and risk of relapse.

An added objective would be to focus on patient-specific factors, including co morbid conditions that may affect an individual's ability to tolerate chemotherapy. Disease-specific ; individual patient and epidemiological factors are to be considered in treatment decisions and undertaking improvisations in those might lend to a significant improvement in outcomes ,considering the socio-economic differences and characteristics of the Indian Public health system(100). Randomized control studies are lacking in view of lack of investigator or sponsored drive.

Population based studies may overcome bias in selection and substitute in some situations for randomization eventually providing valuable data for the scientific assessment of the many problems we struggle with in real world practice(101).

Aims and Objectives:

1. Study the demographic profile of newly diagnosed patients with acute myeloid leukemia at our centre

2. Evaluate treatment and clinical outcome of the above patients treated at our center.

3. Study the role of Wilm's tumour 1 gene expression as a prognostic and MRD (minimal residual disease) marker in acute myeloid leukaemia.

Patients and Methods

This study protocol was approved by our Institutional Review Board (IRB).

This is a descriptive and prospective analysis of newly diagnosed patients with acute myeloid leukemia (AML) diagnosed in the department of hematology at Christian medical college, Vellore.

Duration of the study: 1st of July 2012 till 28th of February 2014.

Definitions

Diagnosis- The diagnosis of acute myeloid leukemia was made according to the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues Fourth Edition(5).

In view of resource constraints the diagnosis of acute myeloid leukaemia was also considered on the basis of Auer rods or morphologic examination.

The presence of ≥ 20% blasts was mandatory either in the peripheral blood or on the bone marrow**.** The presence of < 20 % blasts was acceptable only in those with recurrent genetic abnormalities(5).

Outcomes- These were based on the ELN recommendation in AML (Table I)**(11).**

(Table I) Definition (11, 102) .

Category	Definition
Treatment Response	
Complete remission (CR)	Bone marrow blasts < 5%; absence of extramedullary disease; absence of blasts with Auer rods; absolute neutrophil count > 1.0×10^9/L (1000/μL); platelet count > 100×10^9/L (100 000/μL); independence of red cell transfusions
CR with incomplete recovery (CRi)	All CR criteria except for residual thrombocytopenia (< 100×10^9/L [100 000/μL])or neutropenia (< 1.0×10^9/L [1000/μL])
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi, only included patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Age group	
Paediatric AML	Patients with age≤15 years
Adult AML	Patients between 15-60 years
Elderly AML	Patients ≥60 years
Cytogenetic Risk Group(Refined MRC Criteria)(19)	
Favourable	t(15;17) t(8;21) inv(16)/t(16;16)
Intermediate	Normal; Other non- adverse
Adverse	abn(3q) [excluding t(3;5)] inv(3)/t(3;3) add(5q)/del(5q)/ -5,-7/add(7q) t(6;11) t(10;11) t(9;22) -17abn(17p) with other changes Complex (> 3 unrelated abnormalities) Excluding those with favorable changes
Survival outcomes	
Overall survival	Defined for all patients; measured from the date of diagnosis to the date of death from any cause.
Event-free survival	Defined for all patients; measured from the date of diagnosis to relapse from CR or CRi, or death from any cause.
• Patients whom we could not to contact or establish status were considered dead within 30 days of their last contact for the purpose of this analysis	

Patients:

Inclusion criteria

All patients diagnosed with acute myeloid leukemia and presenting to the department of Clinical haematology at Christian medical college, Vellore were included in the study.

Exclusion criteria

Patients diagnosed as AML with recurrent genetic abnormality [t (15; 17); PML-RARA] were excluded from this analysis.

Methods:

Collection of data:

After approval by the IRB, all patients diagnosed with AML in Clinical Haematology from July 2012 till February 2014 were included.

Demographics- Consecutive patients presenting with the diagnosis of acute myeloid leukemia were interviewed. Demographic information and first contact clinical features were recorded at interview. Details were recorded in a questionnaire format approved by the institutional review board for the study. The demographic data, clinical features and laboratory findings were analyzed for identifying the factors associated with acute myeloid leukemia in our cohort of patients.

Clinical information regarding the treatment regimen, post treatment response, induction deaths, infective episodes and adverse events were obtained from the hospital records (laboratory reports/ physician documentation in hospital charts/hospital discharge summaries).

Re-interview: To determine the status of patients who chose not to proceed with treatment, we additionally attempted to contact all those patients by telephone. At re-interview; details as to type of therapy chosen subsequently, reconfirmation of reason at first contact at our center and time till event (if it occurred), was collected. The telephone numbers for contact were obtained from the hospital records.

WT1 assays: Quantitative levels of WT1 were assessed on newly diagnosed acute myeloid leukemia patients at diagnosis and in those who received treatment, additionally; at the end of induction therapy. However the samples post inductions were limited in view of induction deaths, patient refusal and inadequate sampling. Therefore the WT1 analysis is restricted to pre-treatment diagnosis samples. The paired WT1 samples are planned for analysis at a later date as part of an ongoing study once adequate samples are collected.

Quantitative real-time PCR (RQ-PCR) for WT1

Bone marrow mononuclear cells (BM-MNC) were isolated using Ficoll-paque (GE Healthcare, Foster City, California, USA). Total RNA was extracted from BM-MNCs of AML samples and peripheral blood white blood cells (WBC) of normal controls using Tri Reagent (Sigma, USA). Complementary DNA (cDNA) synthesis was performed with 1µg RNA using Superscript II reverse transcriptase (Invitrogen, Carlsbad, CA, USA) following the manufacturer's instructions. This RQ-PCR assay used the double dye oligonucleotide hydrolysis principle. RQ-PCR assays were performed on ABI 7500 fast platform (Applied Biosystems, Foster City, CA). The generated cDNA was amplified by PCR using a pair of specific primers and a specific internal double dye probe (Fam-Tamra) for WT1 and the control gene ABL. WT1 transcripts were normalized to ABL by using the respective plasmid standards to generate normalized copy

numbers in addition to the ΔCT method. All assays were run in duplicate wells with appropriate non template controls.

For each patient sample the amount of WT1 and ABL expression was determined from the appropriate standard curve generated with each run. WT1 expression, with detectable WT1 copy numbers were expressed per 100 ABL copies.

$$\text{WT1 expression} = \frac{\text{Mean copy number of WT1}}{\text{Mean copy number of ABL}} \times 100$$

Primer probe sequences for WT1 and ABL.

WT1

WT1 Probe: 5'FAM-CAGGATGTGCGACGTGTGCCTGGAG-TAMRA-3'

WT1 RQF: 5'-AGAATACACACGCACGGTGTCT-3'

WT1 RQR: 5'-GATGCCGACCGTACAAGAGTC-3'

ABL

ABL PROBE: 5'FAM-TGCTTCTGATGGCAAGCTCTACGTCTCCT-TAMRA-3'

ABL RQF: 5'-GATACGAAGGGAGGGTGTACCA-3'

ABL RQR: 5'-CTCGGCCAGGGTGTTGAA-3'

- **Data analysis:**

Results were analyzed in terms of the demographic characteristics of newly diagnosed patients collected at first contact. The differences in the profile of above collected characteristics were compared among the treated cohort and those who did not choose to proceed with treatment. We also analysed the characteristics, treatment features, complications and outcomes among those who underwent treatment. These results were compared among different age groups as defined earlier.

The cohort of newly diagnosed patients and those who presented at relapse were analysed separately. The response to treatment was assessed in terms of Complete Remission (CR/CRi), resistant disease and failure/death (Definitions as in table I).

- All patients started on treatment were followed up for treatment related complications including infective episodes and mortality.

- We calculated a WBC index based on the WBC counts at diagnosis and bone marrow blasts using the following formula(103):

- WBC index= $\frac{\text{WBC count in } 10^{9}/\text{L} \times \text{Blast percentage in bone marrow}}{100}$

- The closing date for analysis was 28th of February 2014.

- **Statistics:**

- Descriptive statistics were calculated for all variables. Differences in proportions were assessed using the $\chi 2$ or Fisher exact statistic. Differences in means were tested using a Mann-Whitney-U test or t-test as appropriate. The probability of survival we estimated with the use of the product-limit method of Kaplan and Meier for overall survival and event-free survival and compared by the log-rank test. All survival estimates are reported ± 1 SE.

- The relationships of clinical features to outcome were analyzed by Cox proportional hazard model. All *P* values were 2-sided, with values of .05 or less indicating statistical significance. Statistical analysis was performed using SPSS 16.0 software (SPSS, Chicago, IL).

RESULTS:

A total of 360 patients presented to the department of Clinical Haematology at CMC Vellore in a period of 20 months from the 1st of July 2012 till the 28th of February 2014 with Acute Myeloid Leukemia. Of these, 318 patients were newly diagnosed and 42 patients had presented at relapse (Figure1).

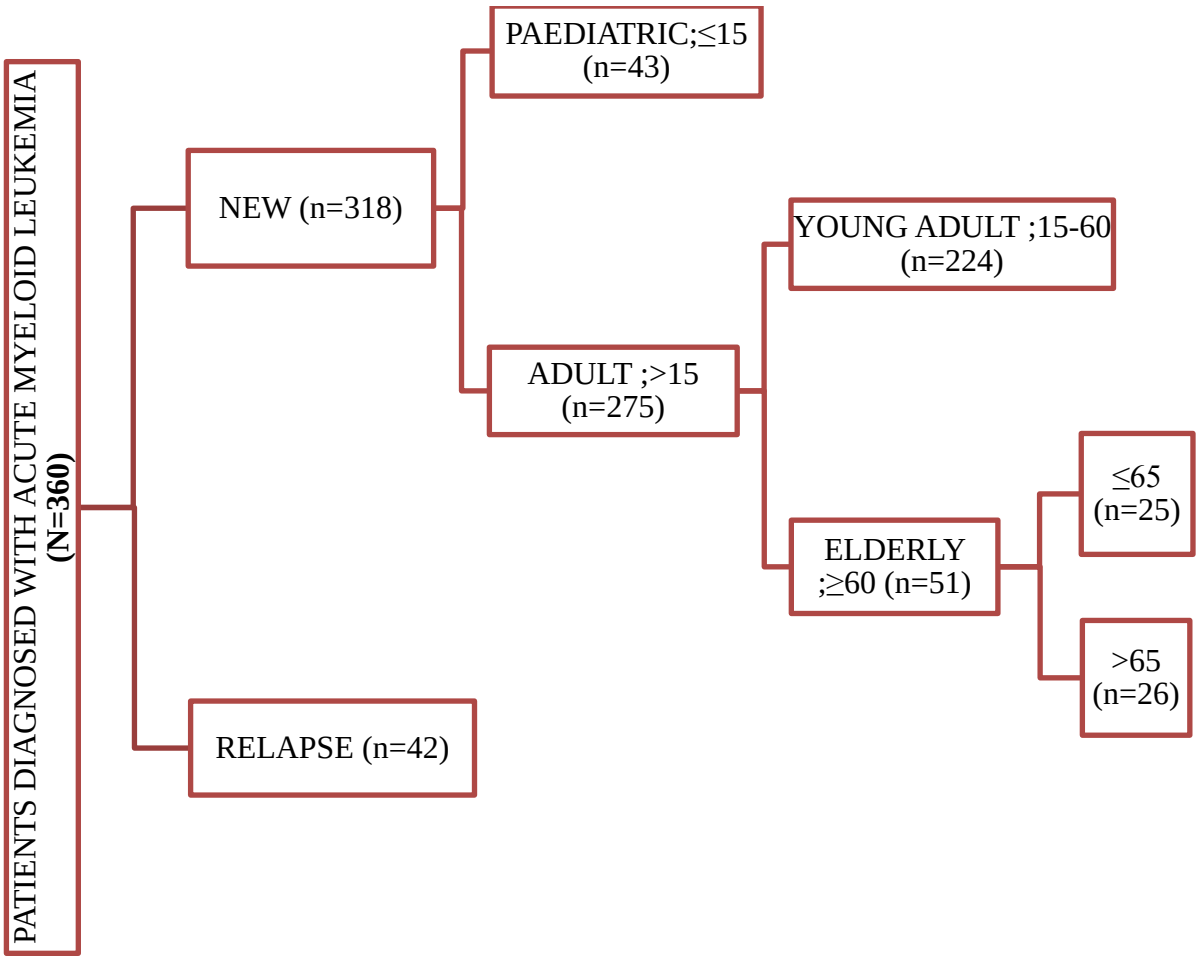


Fig 1: Schematic representation of patients with AML

Baseline demographic characteristics in newly diagnosed patients (Table 1 and Figures 1-3)

The majority of our newly diagnosed patients were adults, 224(70.1%) and male, 212 (66.7%). The median age at presentation of the cohort of newly diagnosed patients was 40(1-79)years with median symptom duration of 4 (1-52) weeks.

When we analyzed the distribution of patients according to the various age groups we observed that the maximum number of newly diagnosed patients were in the 41- 50 age group. There were 39 patients in the 61-70 and 9 patients in the 71-80age group.

The cytogenetic data was available in 214 (67.3%) on newly diagnosed patients. Of these we noted that the intermediate cytogenetic risk group with 148 (69.2%) and AML not otherwise specified, 126(58.9%) were the most common disease related characteristics in our patients. Complex cytogenetics with 28 (13.1%) in the adverse risk group and t (8; 21) in the favourable cytogenetic risk group with 20 (9.3%) patients were the commoner types.

At diagnosis a mean hemoglobin of 77.0 (±23.7) g/L, median white cell count of 14.1 (0.2-920.0)x 10^9/L, platelet count of 36.0 (0.2-920.0)x 10^9/L and a WBC index of 5.6 (0.1-667.8) were the laboratory features noted in these patients.

The median WT1 baseline expression was 13.4 copies/ 10^2 ABL copies.

Table 1: Descriptive baseline demographic characteristics in newly diagnosed patients with AML

Variable	**Patients (N=318) n (%)/ Median (Range)/Mean (±SD)**
Age (years)	40 (1-79)
Sex (Male)	212 (66.7)
Symptom duration (Weeks)	4 (1-52)
Distance from CMC (Km)	600 (10 – 3200)
Treatment at CMC (Yes)	95 (29.9)
Transplant Status (Yes)**	18 (18.9)
Performance Score	**n=311**
0/1	247(79.4)
2	53(17.0)
3/4	11(3.5)
Haemogram	
Haemoglobin (g/L)	77.0 (±23.7)
White blood cell count (x10 ^{9}/ L)	14.1 (0.2-920.0)
Platelet count (x10 ^{9}/ L)	36.0 (2.0-364.0)
Blasts in marrow	**n=288**
Blasts in bone marrow (%)	59.9 (±25.1)
White blood cell Index	7.6 (0.1-667.8)
WT1	**n=90**
WT1(copies/10^{2}ABL copies)	13.4 (0.01-65.03)
Cytogenetic Risk	**n=214**
Favourable	25 (11.7)
Intermediate	148 (69.2)
Adverse	41 (19.2)
Favourable risk subtype	25
t(8;21)	20(9.3)
inv(16);t(16;16)	5 (2.4)
Adverse Risk subtype	41
-7	12 (5.6)
del(5q)	1 (0.5)
Complex	28 (13.1)
WHO classification	**n=214**
With recurrent genetic abnormalities	30(14.0)
With myelodysplasia related changes	53 (24.8)
Therapy related	03 (1.4)
Not otherwise specified	126 (58.9)
Related to Down syndrome	02 (0.9)
**(% derived from patients treated; n=95)	

We analysed the country and state of origin of all newly diagnosed patients. 295 (93%) patients were from India. 21 nationals from Bangladesh and one each from Nepal and Sri Lanka were the patients outside of India who presented to our centre.

The maximum number of patients from India hailed from Tamil Nadu(35%) followed by those from Andhra Pradesh(15%) (Figure 2).

Housewives , students and retired personscomprised the 165 (51.2%) patients who were financially dependent on other members in the family.

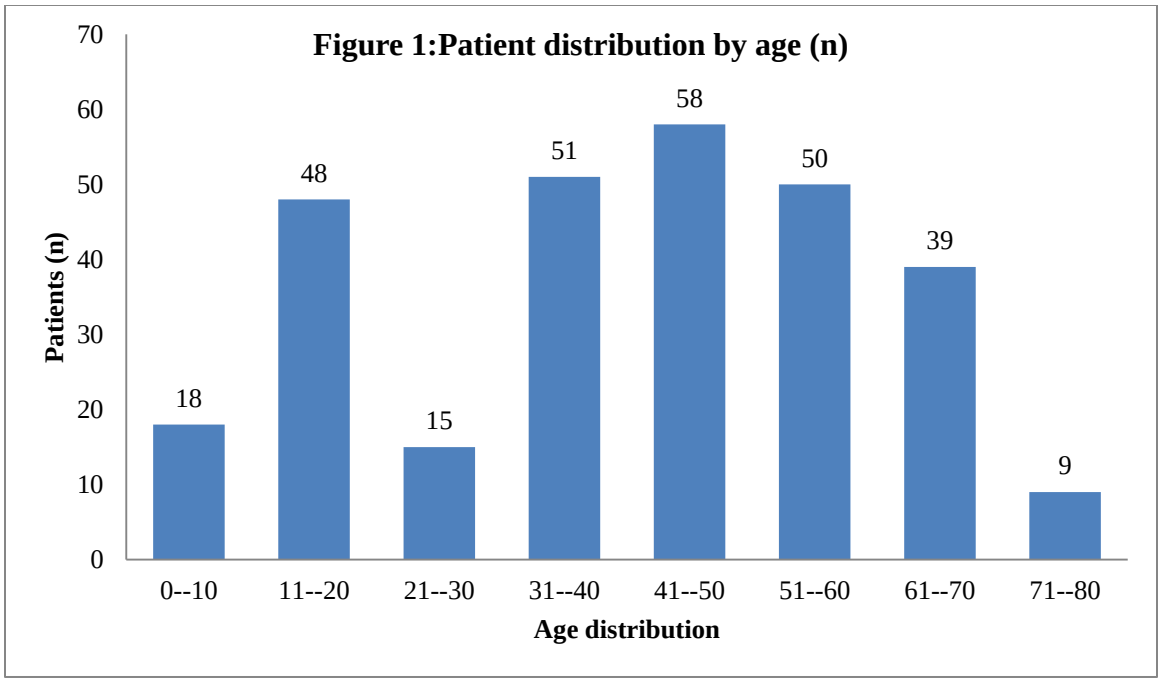


Figure 2:State-wise distribution among newly diagnosed patients (n=295)

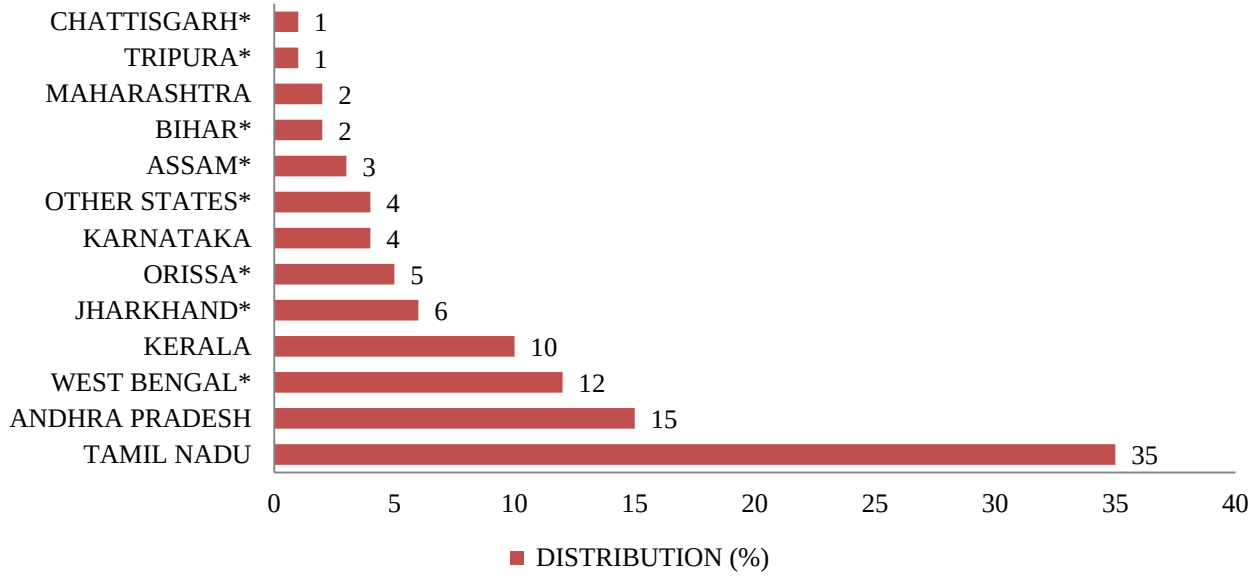
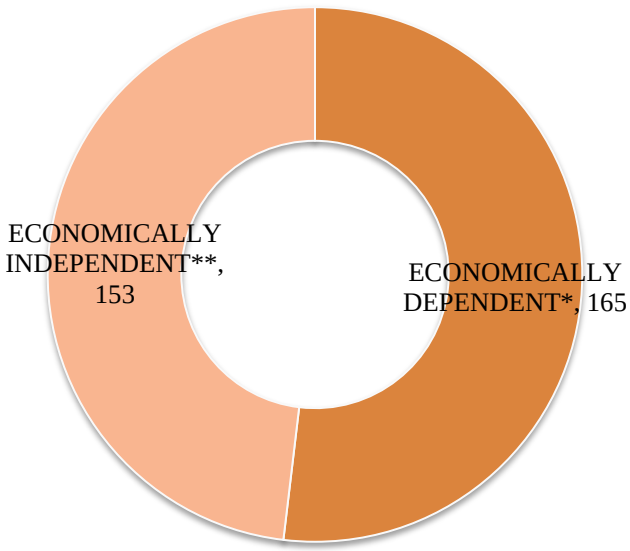


Figure 3: Distribution by financial dependence among newly diagnosed patients N=318



*Housewives, students and retired person were represented in the economically dependent category
**Earning members represent the economically independent category

Comparison among the treated and untreated patients

In our analysis of newly diagnosed patients we observed that only 95(29.9%) patients had treatment at our centre (Table 1). Considering that the majority of the patients did not proceed with treatment, we attempted to analyze the reasons for the same and also to look for any differences in terms of demographic characteristics between these two cohorts.

We first analysed the patient related characteristics, followed by disease related characteristics. Subsequently we compared the two cohorts for demographic parameters which were collected at interview.

Comparison of demographic characters and clinical features among treated and untreated patients (Table 2)

In our analysis the cohort of patients who did not proceed with treatment were older[41(1-79) vs 38(1-68)years], lived farther[700(10-3200)vs 500(20-3000)km], had a poorer performance score[ECOG 2:44(20.4%); 3/4 : 9(4.1%) vs 9(9.5) and 2(2.1)] and were symptomatic for a longer period of time[mean 6.8 vs 5.5 weeks; P=0.002] than those who received treatment.
Feverwas the most common symptom in both the treated and untreated groups. The baseline characterisitics are summarized in table 2.

Table 2: Baseline demographic characteristics and clinical features in newly diagnosed patients (N=318)			
Variable	**Treated patients (N=95) n (%) Median (Range)/Mean ±SD**	**Untreated patients (N=223) n (%) Median (Range)/Mean ±SD**	**P value**
Age (years)	38 (1- 68)	41 (1-79)	0.040
Sex (male)	69 (72.6)	143 (64.1)	0.154
Distance from CMC(km)	500 (20-3000)	700 (10-3200)	0.002
ECOG Performance Status			
0/1 2 3/4	84 (88.4) 9 (9.5) 2 (2.1)	163 (76.0) 44 (20.4) 9 (4.1)	0.034
Symptom		**n=216**	
Symptom duration(weeks) Fever (yes) Fatigue (yes) Bleeding (yes)	5.5 (±6.8) 70 (73.7) 39(41.1) 20 (21.1)	6.8(±6.9) 165 (76.4) 101 (46.8) 38 (17.6)	0.002 0.668 0.387 0.528
Age groups			
Paediatric AML (≤15) Adult AML (15-60) Elderly AML (≥60)	22 (23.2) 63 (66.3) 10 (10.5)	21 (9.4) 161 (72.2) 41 (18.4)	0.002

Comparison of laboratory parameters among treated and untreated patients (Table 3)

The untreated cohort was noted to have a lower mean haemoglobin[75.4(±23.6) vs 84.4(±22.7)g/L;P=0.005] and lower median platelet count [46 (5.0-324.0) vs32 (2.0-364.0) x 10^9/L]in comparison to those who chose to proceed with treatment.

FLT3 and NPM1 positivity was also noted in a higher proportion of patients who did not proceed with treatment. Other features are summarised in table 3.

Table3: Baseline Laboratory parameters in newly diagnosed patients (N=318)			
Variable	**Treated patients (N=95) n (%)/Median (Range)/Mean ±SD**	**Untreated patients (N=223) n (%)/Median (Range)/Mean ±SD**	**P value**
Haemogram			
Haemoglobin (g/L)	84.4 (±22.7)	75.4 (±23.6)	0.005
WBC count (x10 ^{9}/ L)	12.1 (0.7-742.0)	15.3 (0.2-920.0)	0.925
Platelet count (x10 ^{9}/ L)	46 (5.0-324.0)	32 (2.0-364.0)	0.017
Bone marrow blasts	**n=93**	**n=196**	
Blasts in bone marrow (%)	64.8(±24.4)	57.5 (±25.2)	0.620
White blood cell Index	6.8 (0.3 – 451.2)	4.5 (0.1- 667.8)	0.132
Molecular assays			
FLT3/NPM1	**n=83**	**n=44**	
FLT3-/NPM1-	61 (73.5)	27 (61.4)	
FLT3+/NPM1-	3 (3.6)	2 (4.5)	0.030
FLT3-/NPM1+	7 (8.4)	12 (27.3)	
FLT3+/NPM1+	12 (14.5)	3 (6.8)	
WT1	**n=52**	**n=38**	
WT1 (copies/10^{2}ABL copies)	8.8 (0.01-65.03)	19.0 (0.04-61.61)	0.075
Cytogenetic Risk	**n=94**	**n=120**	
Favourable	12 (12.6)	13 (10.9)	
Intermediate	62 (65.3)	86 (71.4)	0.667
Adverse	20 (21.1)	21 (17.6)	
WHO classification	**n=94**	**n=120**	
With recurrent genetic abnormalities	15 (16.0)	15 (12.5)	
With myelodysplasia related changes	28 (29.7)	25 (20.8)	0.083
Therapy related	3 (3.2)	-	
Not Otherwise specified	47 (50.0)	79 (65.8)	
Related to Down syndrome	1 (1.1)	1 (0.8)	

Comparison of socio-economic; medical and family characteristics among treated and untreated patients (Table 4)

We observed that those who did not proceed with therapy were represented by a higher percentage of tobacco [27(12.6%) vs 3 (3.2%); P=0.011] and alcohol users [18(8.4 %) vs 2(2.1%); P=0.044] in comparison those who chose to be treated. Similarly there were more patients in the untreated cohort with exposure to chemicals [23(10.6%) vs 3(3.2%); P=0.027] in comparison to the treated cohort.

The group that proceeded with treatment at our center had a higher representation in ownership of vehicles [63(66.3%) vs 60(27.8%); P=0.001], insurance [7(7.4%) vs 4(1.9%); P=0.039] and access to financial assistance [18(26.3%) vs 6(2.8%); P=0.001].

There was no statistical difference in terms of prior therapy with antibiotics [23(24.2%) vs 47(21.8%); P=0.660], anti-tubercular drugs or food habits [47(49.5%) vs 116(54.0%); P=0.538] among the treated and untreated cohort of patients.

We did not observe any significant statistical difference in the personal and family medical history among the two groups (Table 4).

Table4: Baseline socio-economic; medical and family characteristics in newly diagnosed patients(N=318)			
Variable	**Treated patients (N=95) n (%)/Median (Range)/Mean ±SD**	**Untreated patients (N=211) n (%)/Median(Range)/Mean ±SD**	**P value**
Tobacco (yes)	3(3.2)	27 (12.6)	0.011
Alcohol (yes)	2 (2.1)	18 (8.4)	0.044
Exposure to chemicals (yes)	3 (3.2)	23 (10.6)	0.027
Insurance (yes)	7(7.4)	4 (1.9)	0.039
Financial assistance (yes)	18 (26.3)	4(2.8)	0.001
Residence (yes)	92 (96.8)	206 (95.4)	0.185
Antibiotics (yes)	23 (24.2)	47 (21.8)	0.660
Anti-tubercular treatment(yes)	-	4 (1.9)	0.317
Prior chemotherapy (yes)	9 (9.5)	14 (6.5)	0.355
Vehicle (yes)	63 (66.3)	60 (27.8)	0.001
Air travel (yes)	4 (4.2)	3 (1.4)	0.206
Use of hair dye (yes)	3 (3.2)	19 (8.8)	0.093
Married (yes)	42 (44.2)	138 (61.9)	0.004
Vegetarian (yes)	47 (49.5)	116 (54.0)	0.538
Order of birth	1 (1-5)	2 (1-5)	0.329
Family history			
Diabetes (yes)	5(5.6)	16 (8.0)	0.625
Hypertension (yes)	5(5.6)	10 (5.0)	0.783
Stroke (yes)	-	4 (2.0)	0.314
Heart Disease (yes)	-	3 (1.5)	0.554
Cancer (yes)	6 (6.5)	12 (5.7)	0.795
Medical History			
Diabetes (yes)	13 (13.7)	23 (10.6)	0.446
Hypertension (yes)	6 (6.3)	24 (11.1)	0.226
Stroke (yes)	2 (2.1)	2 (0.9)	0.588
Heart Disease (yes)	-	6 (2.8)	0.183
Other disease# (yes)	19 (20.0)	39 (17.5)	0.999
Prior malignancy (yes)	6 (6.3)	12 (5.6)	0.795
# includes recent surgery/thyroid disorders/developmental disorders/marrow failure/seizure			

Reasons in not proceeding with treatment (Table 5 and 6)

We observed that inability to afford therapy [174 (81.0%)] and lack of a family member [40(18.3%)] to support and stay with the patient for the duration of therapy were the most common reasons in declining the choice to proceed with therapy.

Table 5: Reason for not proceeding with treatment

Variable**	**Patients (N=214) n (%)**
Economic #	174 (81.0)
Family Support##	40 (18.3)
Maintain Quality of life	18 (9.5)
Resignation	11 (5.1)
Consider Alternative therapy	5 (2.3)
Communication handicap due to language barrier	4 (1.9)
Denial of disease	2 (0.9)
Religious restriction to treat	1 (0.5)

**More than one reason allowed
#Inability to meet the costs of therapy represented economic reason ;##Family support was representative of the inability to stay with the patient for duration of therapy

We attempted to contact all patients who had declined to proceed with treatment by telephone. On contact, we re-interviewed the patient/relative regarding the current status of the patient, type of treatment taken subsequently and confirmed the reason in not choosing treatment at CMC.

123 (55.2%) were contacted (Table 6). At re-interview; 107 patients maintained the same reason in not proceeding with therapy. There were 12 (9.8%) patients who reported being discouraged to proceed with therapy as they were counselled regarding the high costs.

Table 6: **Reason for not proceeding with treatment on second contact** #

Variable	**Patients (N=123); n (%)**
Maintain the same reason as at 1st hospital visit	107 (87.0)
Discouraged/Unhappy with counselling	12 (9.8)
Other reasons	4 (3.3)
# 123/223 untreated patients contacted later by telephone	

Characteristics in those proceeding with treatment (Tables 7-9 and Figures 4-6)

Patient and disease characteristics (Table 7)

We noted in our analysis that the majority of those proceeding with treatment were males with a good performance score. There were 17(77.3%), 44(69.8) and 8(80.0%) males in the paediatric, adult and elderly group respectively. In the ECOG performance of 0/1 category; there were 20(90.9%), 57(90.5%) and 7(70.0%) patients in the above groups respectively.

Most of the patients belonged to the intermediate risk based on cytogenetic risk [Paediatric 14(63.6%), Adult 41(66.1%) and Elderly 8(80.0%)]. Based on the WHO classification of AML; across all age groups the most frequent to be treated were the AML not otherwise specified [Paediatric 10(45.5%), Adult 30(48.4%) and Elderly 7(70.0%)].

Other salient features we noted were

- There were no cases of AML with recurrent genetic abnormality in the elderly group.
- The mean haemoglobin, median white blood cell and platelet count was not statistically different across the groups.

Table 7: Patient, disease and treatment characteristics in those proceeding with treatment at CMC				
-	**Paediatric AML (N=22)** (≤15)	**Adult AML (N=63)** (15-60)	**Elderly AML (N=10)** (≥60)	-
Variable	**n (%)/Median (Range) /Mean ±SD**	**n (%)/Median (Range) /Mean ±SD**	**n (%)/Median (Range) /Mean ±SD**	**P value**
Age (years)	12(1-15)	40(17-56)	63.5(60-68)	-
Sex (Male)	17(77.3)	44(69.8)	8 (80.0)	0.684
ECOG Performance score				
0/1	20 (90.9)	57 (90.5)	7 (70.0)	
2	2 (9.1)	4 (6.3)	3 (30.0)	0.162
3/4	0 (0.0)	2 (3.4)	0 (0.0)	
Cytogenetic Risk Group				
Favourable	4 (18.2)	7 (11.3)	-	
Intermediate	14(63.6)	41 (66.1)	8 (80.0)	0.733
Adverse	4 (18.2)	14 (22.6)	2 (20.0)	
Molecular marker(Intermediate)	**n=13**	**n=35**	**n=7**	
FLT3+/NPM1-	2 (15.4)	1 (2.8)	-	
FLT3-/NPM1+	2 (15.4)	3 (8.6)	2 (28.6)	0.089
FLT3+/NPM1+	-	9 (25.7)	3 (42.8)	
WHO classification				
With recurrent genetic abnormalities	5(22.7)	10 (16.1)	-	
With Myelodysplasia related changes	4(18.2)	21 (33.9)	3 (30.0)	0.238
Therapy related	2(9.1)	1 (1.6)	-	
Not Otherwise Specified	10(45.5)	30 (48.4)	7 (70.0)	
Related to Down syndrome	1(4.5)	0 (0.0)	-	
Haemogram				
Hb (g/L)	8.5(±2.3)	8.4(±2.3)	8.5(±2.5)	0.992
WBC count (x10 ^{9}/ L)	23 (1.8-742.0)	10.3 (0.7-346.0)	11.9 (1.1-104.2)	0.116
Platelet count (x10 ^{9}/ L)	42.5 (5.0-324.0)	46.0 (6.0-320.0)	53.0(8.0-196.0)	0.949
Blasts in bone marrow (%)	66.7 (±22.6)	59.3(±25.7)	81.3 (±12.2)	0.090
White blood cell Index	6.9 (1.1-667.8)	6.9(0.3-268.3)	33.8(0.7-94.8)	0.972
Molecular markers	**n=18**	**n=56**	**n=9**	
FLT3-/NPM1-	14 (77.8)	43 (76.8)	4 (44.4)	
FLT3+/NPM1-	2 (11.1)	1 (1.8)	0 (0.0)	0.051
FLT3-/NPM1+	2 (11.1)	3 (5.4)	2 (22.2)	
FLT3+/NPM1+	0 (0.0)	9 (16.1)	3 (33.3)	
WT1	**n=7**	**n=37**	**n=8**	
WT1(copies/10^{2}ABL copies)	1.24 (0.01-24.5)	8.2 (0.01-65.3)	22.5 (2.6-41.1)	0.105

Treatment characteristics (Table8; Figure 4 and 5)

In our analysis of the treatment characteristics, we noted that all paediatric patients [22(100.0%)] were treated in our centre with the AML BFM98 protocol as primary therapy for induction remission. The use of hypomethylating agents use was more frequent in the elderly [Decitabine 4 (40.0%); Azacytidine 2(20.0%)] compared to the adults [Decitabine 5(7.9%); Azacytidine 1(1.6%)]

We also analysed the treatment outcomes in the patients treated. Induction deaths were noted in 5(22.7%), 15(23.8%) and 2(2.0.0%) patients in the paediatric, adult and elderly group respectively; P=0.777. It was observed that CR/CRi was achieved in 13(59.1%), 37(58.7%) and 1(10.0%) patient in the paediatric, adult and elderly group respectively; P=0.005.

In order to estimate the incidence of infections, we analysed the blood cultures in all treated patients sent during admission for remission induction chemotherapy. We noted that in 41(43.0%) patients, blood cultures during febrile episodes were sterile. We also observed that the most common organism in the blood cultures with isolates were [GNB] gram negative bacilli [37(39%)].Carbapenem resistance was noted as a feature in 17(46%) of the GNB isolated.

Table 8: Treatment features in newly diagnosed patients (n=95)

-	**Paediatric AML(N=22)** (≤15)	**Adult AML (N=63)** (15-60)	**Elderly AML (N=10)** (≥60)	-
Variable	**n (%)/Median(Range) /Mean ±SD**	**n (%)/Median (Range) /Mean ±SD**	**n (%)/Median (Range) /Mean ±SD**	**P value**
Treatment Regimens*				
AML BFM 98	22(100.0)	-	-	-
7/3	-	53(84.1)	4(40.0)	
5/2	-	3(4.8)	-	
Decitabine	-	5(7.9)	4(40.0)	
Azacytidine	-	1(1.6)	2(20.0)	
HiDAC	-	1(1.6)	-	
Bone Marrow Transplant (consolidation)	3 (13.6)	14 (22.2)	1 (10.0)	0.505
Treatment Responses				
Induction deaths	5 (22.7)	15 (23.8)	2 (20.0)	0.777
CR/CRi	13 (59.1)	37 (58.7)	1 (10)	0.005
Resistant disease	5 (22.7)	13 (20.6)	5 (50.0)	0.005
Infections – During Induction Chemotherapy				
Negative blood cultures	9 (40.9)	26 (41.3)	6 (60.0)	0.691
Gram Negative Bacilli	10(45.5)	25 (39.7)	2 (20.0)	
Carbapenem Resistant organism	1 (4.6)	14 (20.6)	2(20.0)	0.205
Fungus	8 (36.4)	28 (44.4)	5 (50.0)	0.723

***** 7/3 – Idarubicin12 or daunorubicin 60mg/m^2(3 days) with cytosine 200mg/m^2 as continuous infusion(7 days)
5/2- Daunorubicin 60mg/m^2(2 days) with cytosine 200mg/m^2 as continuous infusion(5 days)
HiDAC-High Dose(3g/m^2) cytosine (q 12 h for 3 days)

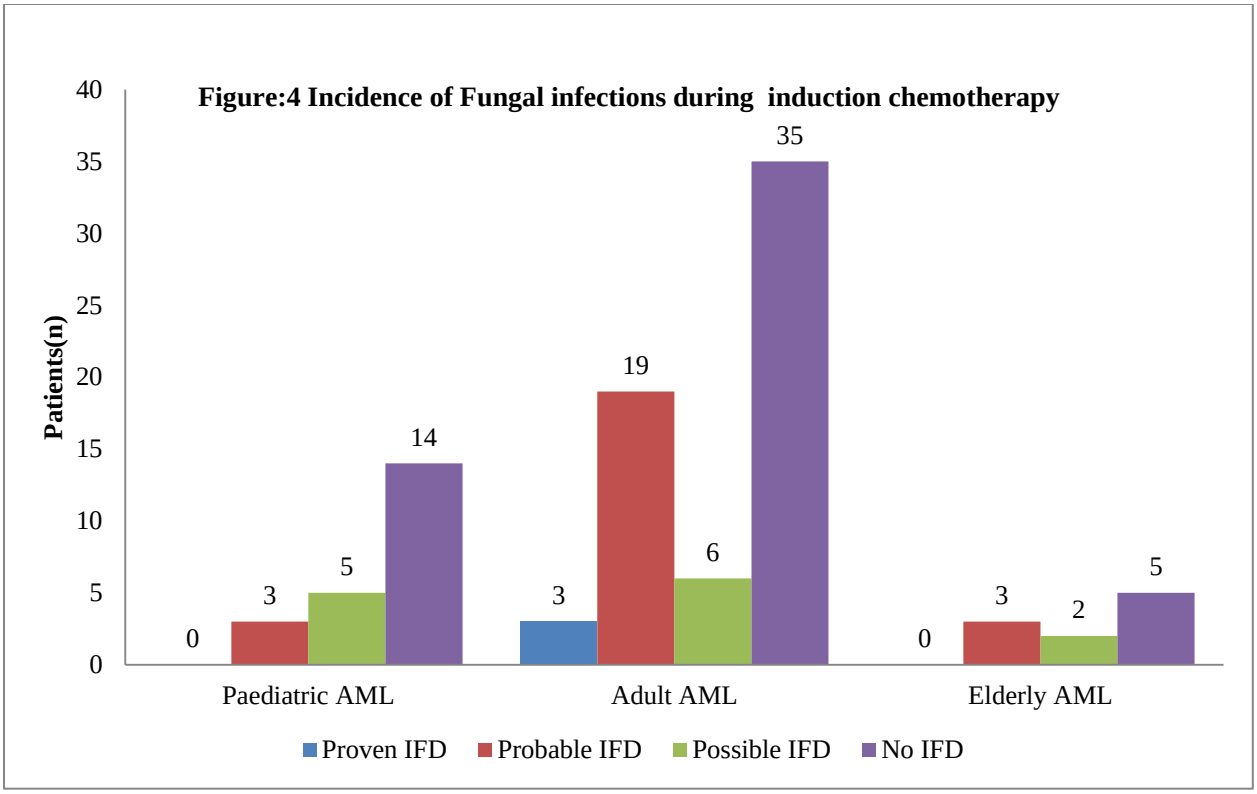


Figure:4 Incidence of Fungal infections during induction chemotherapy
Patients(n)
40
35
30
25
20
15
10
5
0
0
3
5
14
3
19
6
35
0
3
2
5
Paediatric AML
Adult AML
Elderly AML
Proven IFD
Probable IFD
Possible IFD
No IFD

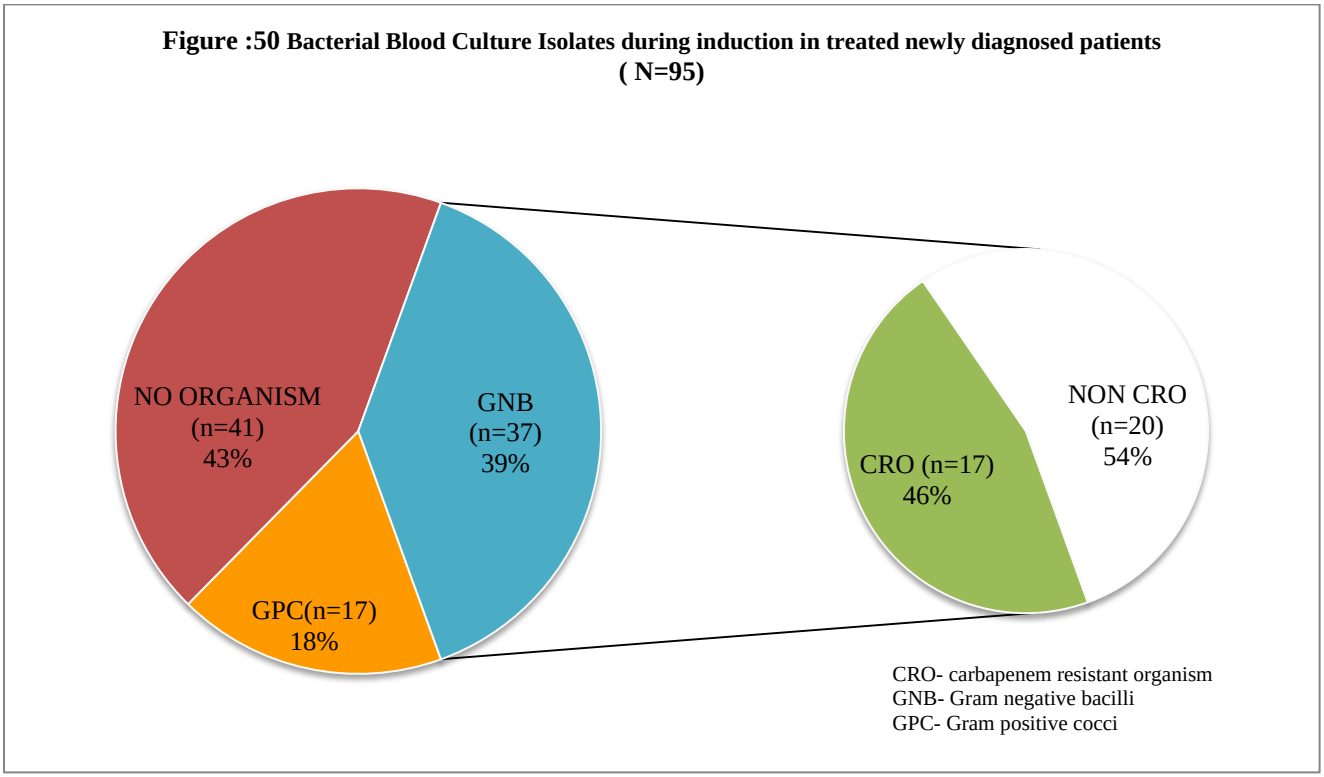


Figure :50 Bacterial Blood Culture Isolates during induction in treated newly diagnosed patients (N=95)
NO ORGANISM (n=41) 43%
GNB (n=37) 39%
GPC(n=17) 18%
CRO (n=17) 46%
NON CRO (n=20) 54%
CRO- carbapenem resistant organism
GNB- Gram negative bacilli
GPC- Gram positive cocci

Causes of induction deaths (Table 9 and figure 6)

In our analysis of the treatment outcomes we had noted that 22(23.2%) patients had died induction. In a further analysis of the causes of death in those who died, we observed that all the 22patients (100.0%) had experienced febrile neutropenia. We also observed that in 14(60.9%) patients, there was a clinical focus of infection of which the most common clinical focus was a sino-pulmonary infection seen in 8(57.2%) patients. We noted that an associated abdominal pain was identified in 10 (43.5%) patients who died.

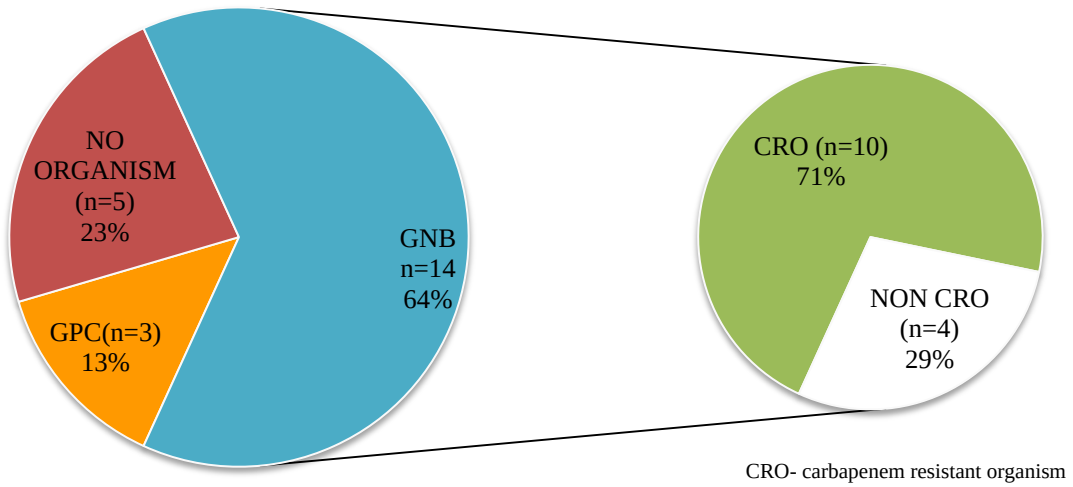
Considering the incidence of neutropenia, we attempted to analyze the incidence of fungal infections. We categorized the fungal infections by the EORTC (European Organization for research and treatment in cancer) criteria as follows (104):

a. Proven IFD: Requiring proof of IFD in diseased tissue for most conditions by demonstration of fungal elements
b. Probable IFD**:** Require that a host factor, clinical features, and mycological evidence be present
c. Possible IFD**:** Includes only those cases with the appropriate host factors and with sufficient clinical evidence consistent with IFD but for which there was no mycological support

In our analysis of induction deaths, invasive fungal disease (IFD) based on EORTC criteria of proven possible or probable was present in 12(52.2%) of patients. Additionally gram negative bacilli (GNB) was the most common organism isolated in patients who expired and 10(71%) were Carbapenem resistant.

Table 9:Causes and features in induction death (n=22)	
Variable	**Patient n (%)**
Febrile Neutropenia	22 (100.0)
Clinical focus of infection (CFI) Sino-pulmonary Gastro-Intestinal Hepatic Skin/soft tissue	14(60.9) 8 (57.2) 3 (21.4) 2 (14.3) 1 (7.1)
Abdominal pain	10 (43.5)
Invasive fungal disease (EORTC*)-IFD Proven IFD Probable IFD Possible IFD	12(52.2) 1(8.4) 8(66.6) 3(25.0)
Bacterial infection in blood culture Carbapenem Resistant organism Others	17(77.0) 10(58.8) 7(41.2)
*EORTC- European Organization for Research and Treatment in cancer definitions for IFD	

Figure :6 Bacterial Blood Culture Isolates in Induction Deaths (N=22)



CRO- carbapenem resistant organism
GNB- Gram negative bacilli
GPC- Gram positive cocci

Comparison of characteristics in newly diagnosed and relapsed patients (Table 10)

We had noted that there were also 42(11.6%) patients who had presented with a disease relapse along with the 318(87.4%) who were newly diagnosed.

We compared the demographic characteristics between the two groups at presentation. In our analysis, the median age of relapsed patients, 38(1-79) was lower than newly diagnosed patients, 40(1-79) years; P=0.022. We observed that 125(58.7%) and 20(64.5%) patients in the newly diagnosed and relapsed cohort had AML not otherwise specified. It was also noted that the intermediate cytogenetic risk group was represented by 147(69.0%) and 22(52.4%) patients in the newly diagnosed and relapsed cohort respectively; P=0.911.

Analysis of laboratory parameters revealed mean haemoglobin in the relapsed cohort was 102.0(±2.9) g/L compared to 77.0(±2.4) g/L in the newly diagnosed; P=0.000.

The other features in comparison are summarized in table 10.

Table 10: Comparison of baseline characteristics among relapsed and newly diagnosed patients with AML			
Variable	**Newly Diagnosed(N=318) n (% of available data)/ Median (Range)/Mean (±SD)**	**Relapsed (N=42) n (% of available data)/ Median (Range)/Mean (±SD)**	**P value**
Age (Years)	40 (1-79)	38 (1-79)	0.022
Distance (Km)	600 (10-3200)	715 (70 – 2400)	0.216
Sex (Male)	212 (66.7)	28 (66.7)	1.00
Age group			
Paediatric AML (<15y)	43 (13.5)	6 (14.3)	0.096
Adult AML (15-60y)	224 (70.4)	35 (83.3)	
Elderly AML (>60y)	51 (16.0)	1 (2.4)	
Treatment at CMC (Yes)	95 (29.8)	25(59.5)	0.000
Transplant Status (Yes)	18 (5.6)	9(21.4)	0.002
Cytogenetic Risk	**n=213**	n=31	
Favourable	25 (11.7)	4 (9.5)	
Intermediate	147 (69.0)	22 (52.4)	0.911
Adverse	41 (19.2)	5 (11.5)	
WHO classification	**n=213**	**n=31**	
With recurrent genetic abnormalities	30 (14.1)	6(19.4)	
With Myelodysplasia related changes	53 (24.9)	5(16.1)	0.687
Therapy related	3 (1.4)	-	
Not Otherwise specified	125 (58.7)	20 (64.5)	
Related to Down syndrome	2 (0.9)	-	
Haemogram	**n=318**	**n=40**	
Hb (g/L)	77.0 (±24)	102.0(±29)	<0.001
WBC count ($x10^9$/ L)	14.1 (0.2-920.0)	6.2 (0.3-241.2)	0.018
Platelet count ($x10^9$ / L)	36 (2.0-364.0)	74.5 (1.0-541.0)	0.004
Bone marrow blasts	**n=288**	**n=38**	
Blasts in bone marrow (%)	59.9(±25.1)	61.6 (±24.3)	0.854
White blood cell Index	5.6 (0.1-667.8)	5.0 (0.3-140.4)	0.719
WT1	**n=90**	**n=16**	
WT1(copies/10^2ABL copies)	13.4 (0.01-65.0)	34.8 (0.86-98.1)	0.019

WT1 expression (Tables 1; 3; 7 and10)

In our analysis of WT1 expression; we observed that the median baseline WT1 expression at presentation was 13.4(0.01-65.03) copies/ 10^2 ABL copies. We also noted that the WT1 expression at baseline was higher in those who did not proceed with treatment compared to the treated [19.0(0.04-61.61) vs 8.8(0.01-65.03) copies/ 10^2 ABL copies].It was observed that across age groups; the expression increased as the group became older. However this was not statistically significant. The expression levels were1.24 vs 8.2 vs 22.5 copies/ 10^2 ABL copies; P=0.105 in the paediatric, adult and elderly age group respectively (Figure 7). We also observed that the expression is higher among patients who present at relapse [34.8 (0.86-98.1)] in comparison to the newly diagnosed patients [13.4 (0.01-65.0) copies/ 10^2 ABL copies]

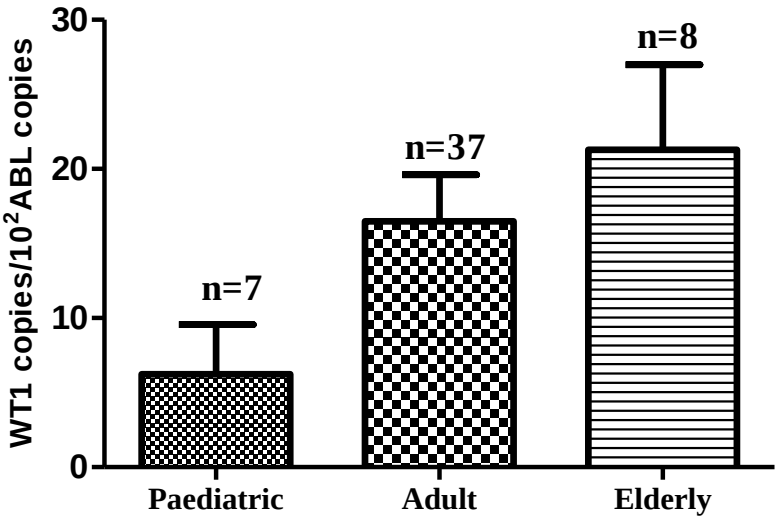


Figure 7: WT1 baseline distribution across age groups

Survival statistics (Figures 8-12)

We analysed the survival of all newly diagnosed patients together and by categorizing them into cytogenetic risk groups and the age groups using the Kaplan –Meier estimates.

OS in newly diagnosed patients (Figure 8)

At the time of analysis the overall survival of the entire cohort including the treated and those not treated was 20.8% ± 2.8% at 12 months with a median follow up of one month. Patients who were lost to follow up beyond a period of 30 days were categorized as dead for the purpose of this analysis.

OS and EFS in newly diagnosed patients by treatment decision (Figure 9a and 9b)

A log rank comparison among treated and untreated showed a statistically significant survival advantage. With a median follow up period of 3months and 1 month for the treated and those that did not proceed with treatment; the one year overall survival was 58.7% ± 6.0% and 7.9% ± 2.1% respectively. (*P value=0.000*)

The Event free survival for the same group at one year with a median follow up period of 3months and 1month was 42.7% ± 7.0% and1.3% ± 1.3% respectively. (*P value=0.000*)

OS and EFS in newly diagnosed patients according to cytogenetic risk (Figure 10a and 10b)

A further analysis of new patients along the cytogenetic risk categories highlighted an improved Overall survival and Event-free survival for the favourable cytogenetics group. With a median follow up period of 5, 3 and 2 months; the one year overall survival for the Favourable,

Intermediate and Adverse risk groups were, 85.7% ± 13.2% ;56.1% ± 7.5% and 47.7%± 13.1% respectively.

The One year Event-free survival for the Favourable, Intermediate and Adverse risk groups were, 85.7% ± 13.2% ;38.2% ± 8.6% and 30.7%± 13.1% respectively with a median follow up period of 5, 3 and 2 months.

There was no statistical superiority in the overall survival *(P value=0.097)*; however the event free survival was superior. There was a significant survival advantage for the favourable risk group over other groups and the intermediate risk group over adverse risk group, (P= 0.041).

OS and EFS in newly diagnosed patients according to age group (Figure11a and 11b)

With a median follow up period of 4, 3 and 2.5 months the One year overall survival for the paediatric, adult and elderly age groups were, 72.1% ± 9.7% ;57.3% ± 7.6% and 52.5% ± 18.6% respectively.*(P value=0.806)*

The One year Event-free survival for the paediatric, adult and elderly age groups were, 45.4% ± 14.2% ;44.5% ± 8.5% and 26.3%± 20.8% respectively with a median follow up period of 4, 3 and 2.5 months;.*(P value=0.759)*

OS in patients presenting at relapse with AML (Figure 12)

When we analyzed survival among those who were treated and those that did not proceed with treatment; the one year overall survival in the treated was 42.7% (± 12.1%) and 10 month overall survival in those who did not proceed with treatment was 13.7% (± 0.9%) ;at a median follow up period of 9and 1month respectively; (*P value=0.005*)

Survival curves in figures

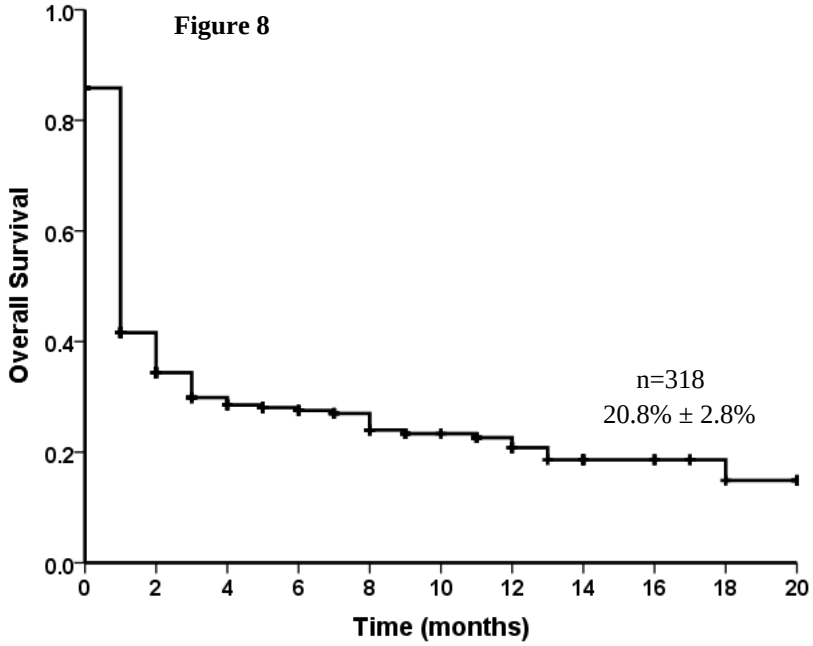


Figure 8: Kaplan Meier curve for overall survival in newly diagnosed patients with AML (n=318).
The One year OS was 20.8% ± 2.8% at a median follow up of 1 month.

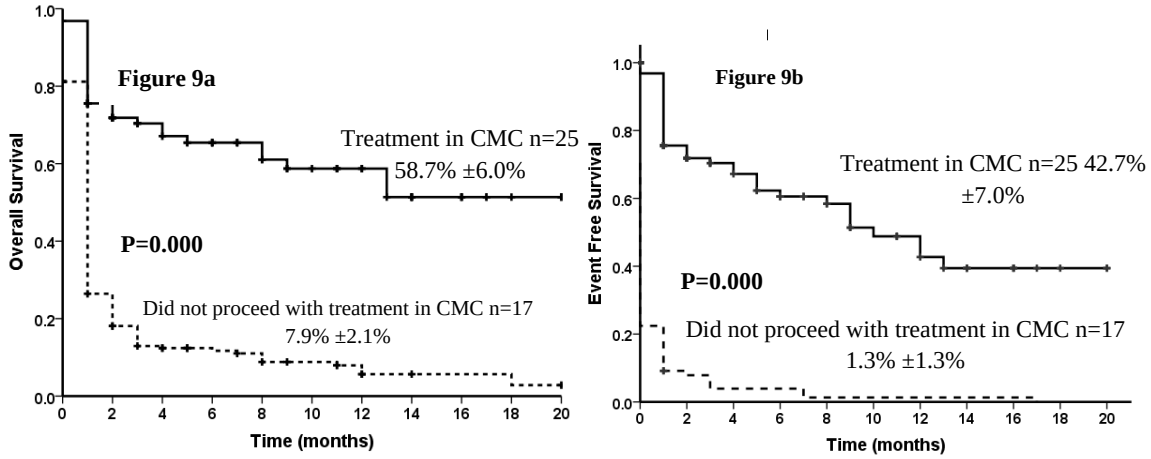


Figure 9a: Kaplan Meier curve for OS of newly diagnosed patients by treatment decision.
With a median follow up period of 3months and 1 month for the treated and those that did not proceed with treatment; the one year overall survival was 58.7% ± 6.0% and 7.9% ± 2.1% respectively. (*P value=0.000*)

Figure 9b: Kaplan Meier curve for EFS of newly diagnosed patients by treatment decision.
With a median follow up period of 3months and 1 month for the treated and those that did not proceed with treatment; the overall survival was 42.7% ± 7.0% and 1.3% ± 1.3% respectively. (*P value=0.000*)

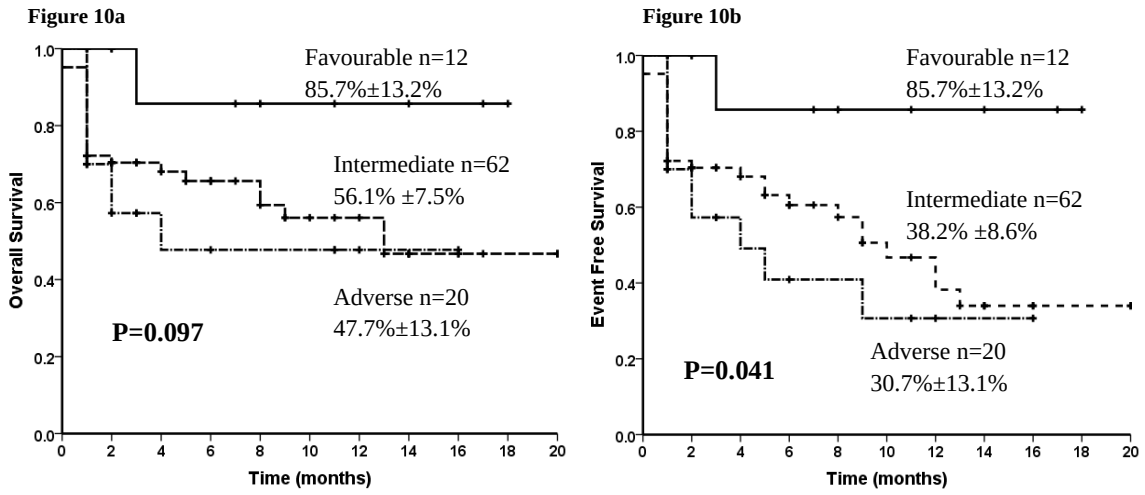


Figure 10a: Kaplan Meier curve for OS in treated newly diagnosed patients according to the cytogenetic risk.
With a median follow up period of 5, 3 and 2 months; the one year overall survival for the Favourable, Intermediate and Adverse risk groups were, 85.7% ± 13.2% ;56.1% ± 7.5% and 47.7%± 13.1% respectively.*(P value=0.097)*

Figure 10b: Kaplan Meier curve for EFS in treated newly diagnosed patients according to the cytogenetic risk. With a median follow up period of 5, 3 and 2 months; the One year Event-free survival for the Favourable, Intermediate and Adverse risk groups were, 85.7% ± 13.2% ;38.2% ± 8.6% and 30.7%± 13.1% respectively. There was a significant survival advantage for the favourable risk group over other groups and the intermediate risk group over adverse risk group (*P value=0.041*).

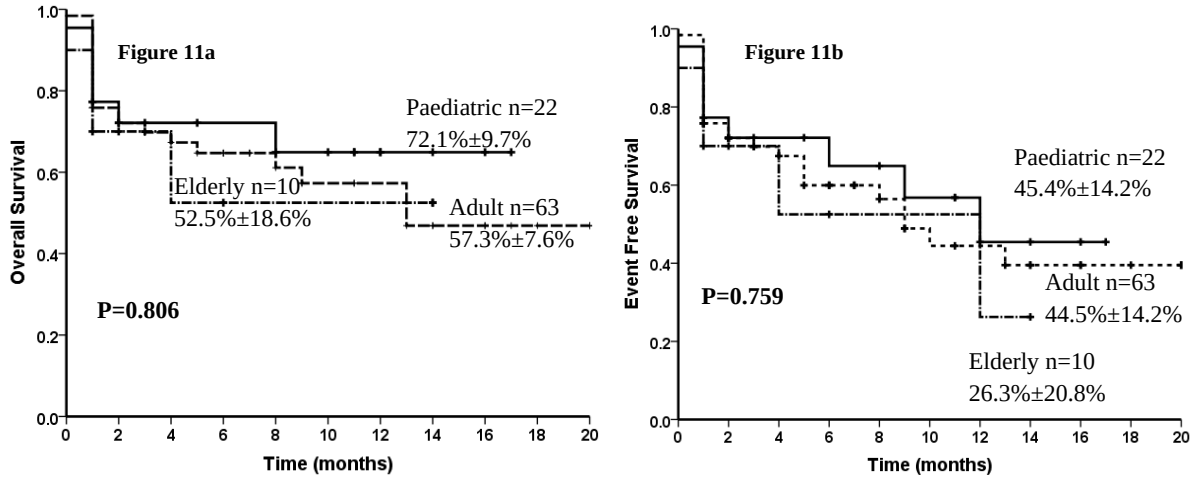


Figure 11a: Kaplan Meier curve for OS in treated newly diagnosed patients according to the Age group.
With a median follow up period of 4, 3 and 2.5 months the One year overall survival for the paediatric, adult and elderly age groups were, 72.1% ± 9.7% ;57.3% ± 7.6% and 52.5%± 18.6% respectively.*(P value=0.806)*

Figure 11b: Kaplan Meier curve for EFS in treated newly diagnosed patients according to Age group.
With a median follow up period of 4, 3 and 2.5 months ; the One year Event-free survival for the paediatric, adult and elderly age groups were, 45.4% ± 14.2% ;44.5% ± 8.5% and 26.3%± 20.8% respectively.*(P value=0.759)*

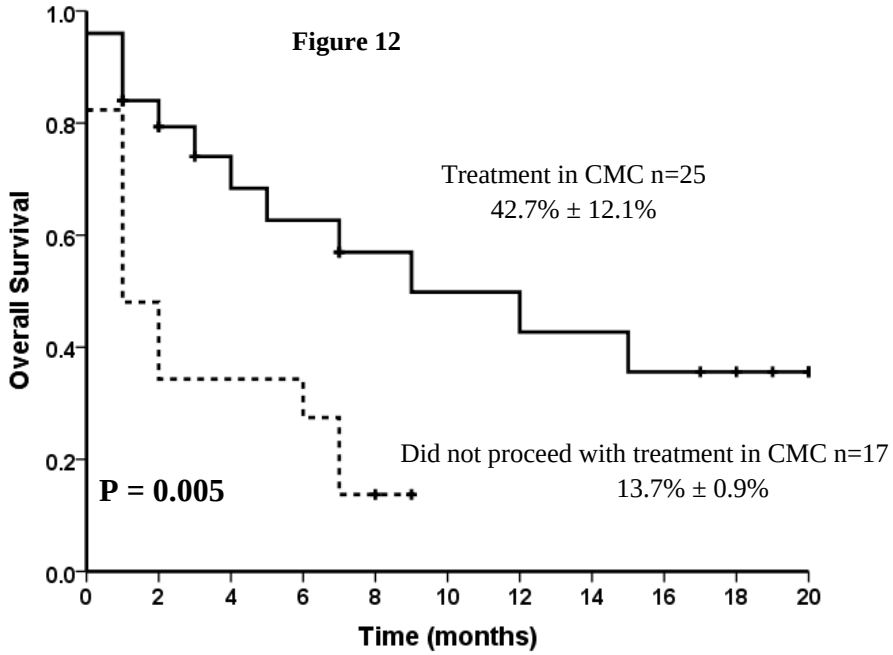


Figure 12: Kaplan Meier curve for OS stratified by treatment decision in patients presenting at relapse. The overall survival in the treated and those who did not proceed with treatment were 42.7% ± 12.1%at one year and 13.7% ± 0.9% at 10 months ;at a median follow up period of 9and 1month respectively; *P value=0.005*

Discussion

Acute myeloid leukemia is described as a disease of the elderly with a median age reported from 69 to 72 years (38, 105). Outcomes are cited to be improving, more to the advances in supportive care than to any therapeutic break-through(106). The patterns of haematological malignancies may reveal geographical differences which need to be accurately studied to enable a better understanding (107, 108).There is however, a lack of data on the demographic profile and clinical outcomes in patients with Acute myeloid leukemia from India.

Demographic data

The median age of incidence in AML observed in our study is 40(1-79) years. This is earlier by three decades, what is reported in literature based on registries from Europe and America (14, 109).On the basis of age and incidence rates, it is postulated that there are cumulative pathogenetic events in AML whereas the flat incidence rates in ALL and APML, lends support to fewer pathogenetic events (38).Our observation is similar to other reports from Asia where the median age is reported lower than the western population (110-112).This might suggest alternative disease biology in our patients. A male preponderance of 224(66.7%) patients is noted in our study. This is comparable to the male excess in AML reported in literature (38, 113). A greater exposure to carcinogenic events is a postulation (114). Additionally ;gender related health care distance propagated by the chronic neglect of women in India; might amplify this gender disparity(85, 115).

The inadequacy of medical infrastructure in India has been frequently reported(85). It is noted in the case of other medical interventions that distance to health care facilities is a significant barrier to availing treatment(116).The median symptom duration of 4 (1-52) weeks and distance

travelled of 600(10-3200) km is possibly a reflection of the same. Our patients hailed from Tamil Nadu to as distant as Tripura. Many of our patients were from the East and North-East India who have limited health care access(117). Treatment areas being distant; patients develop a tendency to postpone their assessment for a later date(85, 118).

Laboratory and disease related features in newly diagnosed patients.

The mean haemoglobin of 77.0(±23.7) g/L; white blood cell count of 14.1 (0.2-920.0) x 10^9 /L; and the platelet count of 39.0 x 10^9 /L at presentation in our analysis, is lower than reports from other countries (14, 112). We postulate that this could be due to the national tendency to delay the decision to seek appropriate care(119, 120). The intermediate cytogenetic risk group with 148 (69.2%) and AML not otherwise specified with 126 (58.9%) patients were the most frequent disease characteristics noted. This is consistent with observations from other centers (111, 121, 122) . However in comparison to reports categorizing AML by the WHO classification we observed a lower number of patients[25(11.7%)] with recurrent cytogenetic risk(123).This we postulate to the study design to exclude patients with t (15;17).

Differences among patients who proceed with therapy and those who decline treatment.

Differences in demographics

A total of 95 (29.8%) patients decided to proceed with treatment at our center, This is strikingly lower than that reported from western countries where the access to free government sponsored health care is higher(124).In our analysis we noted that that those who declined therapy were older(41 vs 38 years ;P=0.040) and travelled from farther (700 vs 500 km;P=0.002). The young and those with lower performance scores were better represented in the treated group

(P=0.034).There is no such criteria in our hospital's decision to treat patients, and the above selection bias might be reflective of the informed decision process.

We also observed that those who did not proceed with therapy were represented by a higher percentage of tobacco [27(12.6%) vs. 3 (3.2%); P=0.011] and alcohol users [18(8.4 %) vs 2(2.1%); P=0.044].This could reflect a possibility that those who did not proceed with treatment represented the poorer sections of our society(125).Reflective of the better economic standing in patients who choose to proceed with therapy; we observed that this group had a higher ownership of vehicles [63(66.3%) vs 60(27.8%);P=0.001], insurance [7(7.4%) vs 4(1.9%); P=0.039] and financial assistance [18(26.3%) vs 6(2.8%); P=0.001]. We did not observe any significant statistical difference in the personal and family medical history among the two groups (Table 4).

Laboratory and disease related differences in newly diagnosed patients.

The lower mean haemoglobin of 75.4(±23.6) vs 84.4 (±22.7) g/L;P=0.005, platelet count of 32.0 (2.0-364.0) vs 46 (5.0-324.0) x 10^9 /L; P=0.017, might be reflective of an advanced disease presentation in the cohort who did not proceed with treatment. There were no significant differences in the disease risk or WHO classification among the two groups.

Decision patterns in declining therapy.

Decision behavior is influenced by various factors(126) .We observed that inability to afford therapy[174 (81.0%)] and lack of a family member [40(18.3%)]to support and stay with the patient for the duration of therapy were the most common reasons in declining the choice to proceed with therapy. Other reasons which we observed in our study are noted in table 5. The

need to a maintain a similar quality in life as a reason for deferring therapy has been noted with other diseases(127).

On re-interview we observed that 16(13.0%) patients attributed a different reason to the one they administered at first visit. The commonest explanation being counselling driven; is a possible reflection of the health care approach in India(128).

Characteristics of patients who underwent treatment:

We did not observe any statistically significant differences across the various age groups in relation to patient and disease characteristics. The Elderly cohort had a higher representation of patients with poorer performance scores, higher platelet count and WBC Index. **(P<0.05)**

In our analysis there was no patient in the Elderly cohort with favourable cytogenetics. This is in contrast to observations from other registries where the incidence of favourable cytogenetics is constant with age(129). Our findings are similar to recent data from the Swedish registry where the incidence of the favourable karyotype decreased with age (130). Our observations with mean haemoglobin, white blood cell and platelet count are lower than those reported from the SWOG trial data, however the marrow blast percentage was similar to their observations(14).Across age groups; it was observed that the WT1 expression increased as the group became older. The expression levels were1.24, 8.2 and 22.5copies/10^2 ABL copies (P=0.105) in the paediatric, adult and elderly respectively.

Treatment features:

The conventional 7+3 regime is the most commonly used therapeutic protocol in induction in Adults and the Paediatric AML BFM 98 in patients' ≤ 15 years at our centre. The Elderly group had a higher representation of patients on hypomethylating agents.

There were 13(59.1%), 37(58.7%) and 2 (20%) patients who attained CR following first cycle of induction in the paediatric, adult and elderly groups respectively. Those who had a resistant disease, defined as those who failed to enter CR after the first course of induction chemotherapy were 5(22.7%), 13(20.6%) and 5(50%) respectively in the paediatric, adult and elderly groups. These results are lower than those reported from the SWOG trial dataset with 60% and 31% respectively(14). Similar treatment outcomes have been reported from the university hospital ,Brazil (131).In our analysis the induction death occurred in 5(22.7%), 15(23.8 %) and 2(20.0%) across the age groups. A recent analysis of patients enrolled in trials at the SWOG and MDACC receiving intensive therapies from 1991-2009 reported a sharp decline in treatment related mortality(3%-4%) from 2006-2009(106). The higher rate of bacteremia and infection with fungus and multidrug resistant strains in our analyses might be possible reasons for such striking differences in observation. We also recognize that unlike above reports, our study is not in the setting of a clinical trial. We noted 56(57%) patients to be bacteremic .Gram Negative Bacilli were the predominant isolate in them and of these 17(46%) were carbapenem resistant organisms. Such high rate of carbapenem resistance is a cause for worry. Another major concern along with bacterial infections is the changing trends in fungal disease in developing countries(132).We also noted that Invasive fungal disease was associated with 12 (52.2%) of the induction deaths. This is comparable to attributable mortality rates reported from an earlier study by Pagano et al(133). Our observations on infections are strikingly higher than what is reported from other centers.

The Japanese Acute Leukemia Group identified bacteremia in 9.5% cases with gram positive cocci (49%)as their major isolate(134).The higher incidence of gram positive organisms was also noted by the Polish Acute Leukemia Group(135). The incidence of carbapenem resistant

organism by the European group for blood and marrow transplantation of 5-14% is also contrastingly lower (136) .However our resistant rates are comparable to reports from other centers in India where a prevalence of 40-50% in enterobacteriace has been noted(137).

WT1: Role in prognosis

We observed that the median baseline WT1 expression at presentation was 13.4(0.01-65.03) copies/ 10^2 ABL copies. This is lower than reports from European Leukemia net and Italy where the median values obtained were 25.5 and 93.6copies/ 10^2 ABL copies respectively(65, 138).Across age groups; it was observed that the expression increased as the group became older. However this was not statistically significant. The expression levels were1.24 vs 8.2 vs 22.5 copies/ 10^2 ABL copies; (P=0.105) in the paediatric, adult and elderly age group respectively.

The WT1 expression at baseline was higher in those who did not proceed with treatment. The WT1 expression though not statistically significant (P=0.075) was noted to be higher in the cohort which did not receive treatment at CMC (19.0 vs 8.8 copies/10^2 ABL copies).

We also noted that it was higher in those who presented at relapse [34.8 (0.86-98.1)copies/ 10^2 ABL copies] compared to the newly diagnosed. This is a statistically significant observation; (P=0.019). Higher WT1 expression might relate to a higher disease burden (138, 139).

In order to derive the role in our subset of patients more numbers and paired assays at different time points in treatment are required.

Comparison among patients who present at relapse and newly diagnosed patients.

This comparison revealed that; at relapse, patients presented with a higher haemoglobin (10.32 vs 7.8) and platelet count (74.5 vs 36.0 x 10^9/L). There are no biological explanations to this

observation. This might relate to a self-selection bias in this group of patients who at relapse seek medical attention earlier(140).There was no difference in the cytogenetic or WHO classification based disease characteristic.

Survival statistics

We analysed our survival data on the basis of treatment decision, cytogenetic risk and age group. The overall survival of 20.8 %(±2.8%) might be reflective of the study design where patients not contactable were considered dead. Our survival in newly diagnosed patients is lower than survival reported in the AML 96 and a polish trial evaluating cladribine in AML (141, 142) . The survival is comparable to CALGB report of median survival of 1.2 months (20).

We noted a significant advantage in event free survival for the favourable cytogenetic risk group over the others (P=0.000). The Elderly and those with adverse cytogenetics had the least EFS and OS among those treated. (Figures 7-14)

These observations are consistent with survival patterns reported across registries and other centers (11, 20, 143).In the analysis of patients who received treatment at relapse we noted a median OS of 9 months and a one year OS of 42.7 %(±12.1%). These are higher than what is reported in literature; however this needs to be interpreted in consideration with the short duration of follow up. Rowe and colleagues had reported a 5 year OS of 11% based on the ECOG data(144).

Various demographic observations reported in literature have been tabulated for comparison (Table II).

Table II: Comparison of demographic features in patients with AML reported in literature

Study center/ country	Period	N	Age (y)	Blast (%)	Hb (g/L)	TLC (10^9/L)	Platelet (10^9/L)	Adverse Karyotype	ECOG 0/1(%)	Induction death (%)	CR (%)
SWOG(14) USA	**1990-1996**	968	-	70*	92*	19*	49*	33*	77	12	50
MDA(106) USA	**1991-2009**	470	56	-	-	05	45	-	86	4	-
SWOG(106) USA	**1991-2009**	498	49	-	-	13	55	-	87	3	-
FHCRC(145) USA	**2008-2011**	116	57	-	-	-	-	20	87	-	68
MRC12(146) UK	**1994-2002**	2934	41	-	-	14	-	15	88	-	85
Sweden(38) SWEDEN	**1997-2005**	2767	72	-	-	-	-	23	53	10	65
JALSG(111) JAPAN	**1997-2001**	638	45	-	83	14	52	8	-	-	-
AKU(147) PAKISTAN	**1988-1996**	74	38	-	83	49	65	-	65	29	-
Haryana INDIA(148)	**2008-2012**	220	28		85	44	67	-	-	-	-
TMH(74) INDIA	**1998-2000**	260	27	57	68	-	63	-	-	-	-
CMC** INDIA	**2012-2014**	318	40	60	77	14	36	19	79	23	53

SWOG, South West Oncology Group; **MDA**, MD Anderson Cancer centre; **FHCRC**, Fred Hutchinson Cancer Research Centre; **JALSG**. Japanese Acute Leukemia Study Group; **AKU**, Aga Khan University; **TMH**, Tata Medical Hospital; **CMC**, Christian Medical College ;*only inclusive of patients <56 years;**Present Study

Limitations of the study

We report on potential limitations that could affect the interpretation of our results.

This study and its conclusions are based on the data derived from a single tertiary care institute and could lead to clustering of cases, not representative of the entire population. Also, conclusion on treatment features and outcomes is limited by the small proportion of patients proceeding with treatment and the limited follow up. We also recognize that there are multiple overlapping questions and reasons (for not proceeding with treatment in the questionnaire). A narrowing of different reasons into fewer themes; would enable better understanding of the decision behavior in our patients. Also, recruiting information at times of patient crises lends to compromise in objectivity of some answers. We recognize that the small numbers and absence of paired post induction samples limit the interpretation of our WT1 results.

A prospective study which is multi-centric, with larger numbers, more objective questioning, pairing of post therapy samples with the diagnostic marrow samples and longer duration of follow up could be ideal in deriving the demographic and clinical outcome of our patients.

Conclusions

The median age of patients with AML in India noted in our study is three decades earlier than that reported in the literature. We noted that less than one third of our patients proceed to treatment after diagnosis. In comparison to those who are treated, patients who do not proceed with treatment have more adverse clinical, disease and laboratory features. Importantly, the inability to finance treatment costs and inability to accompany the patient for the duration of therapy were the main reasons in declining therapy identified in our study.

In our analysis of treatment related features, 7+3 regime is the most commonly used therapeutic protocol in induction in Adults and the Paediatric AML BFM 98 in patients' $\leq$ 15 years at our centre. We also observed that age group and cytogenetic risk are predictive of treatment outcomes in our population. A major concern is the incidence of infections both bacterial and fungal, higher than reported in literature. We also report on induction death which is higher than that cited in literature with invasive fungal disease being present in greater than 50% of individuals who died during induction.

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Annexure - Questionnaire

GENERAL DEMOGRAPHIC:

Name | Patient ID/ UPN

Sex: | Year of birth:

State | Country

Insured- Yes/No | Company/other sponsored- yes/no

Distance from hospital (Approximately):

Birth order **1.**First **2.**Second **3.**Third **4.**Fourth **5.**Fifth or >

SOCIO- ECONOMIC HISTORY:

Monthly income:

Type of work:

Office worker	☐	Managerial/administrative	☐
Health worker	☐	Daily wages	☐
Self employed	☐	Agriculture/labourer	☐
Equipment operator	☐	Factory worker	☐
Home maker	☐	Student-school	☐
Retired	☐	Other	☐

If other; Details:

Residence : Owned ☐ Rented ☐ Personal vehicle: - Yes / No

PERSONAL & FAMILY HISTORY:

Personal history: Tobacco: Yes/No Alcohol: Yes/No Vegetarian: Yes/No

Previous cancer: Yes/No If Yes; Treatment received : Surgery/ RT/ Chemotherapy/ Others

Siblings(number) Children(number)

Family history of cancer: If Yes; Details:

TREATMENT HISTORY (CURRENT ILLNESS):

Predominant symptoms (multiple ticks allowed)

a. Fever ☐ b.Breathlessness ☐ c. Fatiguability ☐
d. Petechiae ☐ e. Bleeding ☐ f. Others ☐
g. If others: Details:

Duration of symptoms: 1. <1wk 2. 1-2 wk 3. 2-4 wk 4. 4-8 wk 5.> 8 wk

Treatment - Antibiotics ☐ ATT ☐ Antineoplastic agents ☐ Transfusion- Yes/ No

PERFORMANCE SCORE

ECOG		Definitions
0		Asymptomatic
1		Symptomatic, fully ambulatory
2		Symptomatic, In bed less than 50% of the day, but not bed ridden
3		Symptomatic, in bed more than 50% of the day but not bedridden
4		Bed ridden

TREATMENT PLAN

Conventional treatment- Yes/ No Curative/Palliative

Reasons for not proceeding with treatment

Religious		Lack of social support	
Economics		Fear of side effects	
Cultural		Resignation	
Alternative therapy		Denial	

If other; Details: